Clinical and ethical aspects of modulating behaviour and affect through Deep Brain Stimulation

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Foreword & Acknowledgement

I'm pleased to present this cumulative dissertation on clinical and ethical aspects of studying behaviour in disorders that have been treated with deep brain stimulation. This work bridges disciplines of (clinical) neurobiology, (moral) psychology and ethics. My interest in the neurobiological underpinnings of behaviour has been a loyal companion since I conducted ethological experiments in preclinical psychiatric research during my time as a master student. Based on my early interest in philosophy reaching to the beginning of my studies as a biologist, I felt the urge to explore the realm of intentions by leaving behind the mechanistic realm of operant conditioning. Hence, the temptation of understanding behaviour and how ethics informs and reflects on neurobehavioural research was present ever since. In essence, the central topic is one of neuroethics that is dedicated to interlocking the excitement of advances in basic and clinical neuroscience with human values and the diversity of our societies. In addition, I always felt the importance of actively evaluating research through an ethics lens and probably today more than ever before.

This cumulative dissertation has been a collaborative and international effort. My gratitude goes to all who have supported me during my research in the last years: I thank Prof. Nikola Biller-Andorno of the Institute of Biomedical Ethics and History of Medicine (IBME)) for accepting me as a PhD-student in her institute, PD Dr. Markus Christen (IBME), Prof. Christian Baumann (University Hospital Zurich, Department of Neurology, USZ) and Dr. Oguzkan Sürücü (University Hospital Zurich, Division of Neurosurgery, USZ), my supervisors, for their unconditional support and the provision of a welcoming environment, being it at the institute or at the hospital (e.g. when attending surgeries). Their help was truly fundamental for completing this PhD. Mirroring the studied topic, deep brain stimulation, this PhD has been a multidisciplinary effort and I'm incredibly thankful for their priceless expertise.

I also thank Prof. Walter Glannon (University of Calgary) to whom I owe a great debt of gratitude for his support in philosophical reflection and the felt enjoyment of constant exchange. I thank Prof. Carmen Tanner (Zeppelin University, Germany) for her expertise on moral-psychological research and her dedication, Prof. Yasin Temel (Mastricht University, the Netherlands) for his expertise on neurosurgical issues, Prof. Christopher Pryce (Psychiatric University Hospital Zürich; PUK) and Hannes Sigrist (PUK) for their loyal support and the possibility of conducting exciting preclinical translational research, Dr. Sabine Müller (Charité Universitätsmedizin Berlin) for her support in Neuroethics and finally, Dr. Daniela Noain (USZ), Dr. Sophie Masneuf (USZ) and Dr. Fabian Büchele (USZ) for their kind integration in preclinical DBS-research and their sharing of expertise. Finally, I thank my family for their constant support which was essential for completing this PhD: Eva Ineichen, my mother, Beat Ineichen, my father, my brother Yves Ineichen and my girlfriend Mena Malacrida.

My interdisciplinary background together with the support from all the above listed experts from various fields led me to value the unique opportunity for cross-fertilization of ideas, particularly through interactions with colleagues representing different areas. The support from so many renowned experts can certainly not be taken for granted and filled me with great honour.

Part I Introduction

Human brain research has gained tremendous momentum in recent years and unquestionably will continue emerging as a result of our ability to record, image and modulate brain processes. As our knowledge about fundamental brain processes increases, clinical neuroscience advances at a rapid pace. As a result, it might often be necessary to step back for a while to give room to both carefully reflect on how the field is developing and critically appraise knowledge gains and their therapeutic applications.

Section I: Clinical aspects of modulating behaviour and affect through Deep Brain Stimulation

SUMMARY:

The papers which are part of this cumulative dissertation have in common that they discuss DEEP BRAIN STIMULATION (DBS) for investigating clinical and ethical aspects of neuromodulation interventions with a particular emphasis on assessing complex behavioural and affective changes. First, I will outline the intervention itself combined with the clinical relevance of this type of intervention and a preview on technological developments. Secondly, I outline the significance of DBS for basic research and clinical neuroscience together with some recent notions on how unwanted behavioural and affective side-effects might emerge. Finally, I briefly outline the connection between the basal ganglia (i.e. the neuroanatomical loci most frequently used in DBS interventions) and their role in establishing certain behaviours and emotions. In summary, I argue that given the clinical relevance DBS holds and the still unknown mechanism of action, DBS has revealed more about how the brain works than how DBS works and this particularly through successful electrophysiological research. Besides other important investigations, such research brought back to the fore the importance of electrophysiological processes in human brain research. Given the emphasis on electrophysiology, performed research in recent years contributed to new disease models emphasising the network architecture of the human brain. Next, I argue that the difficulty of stimulating a given target with the requisite precision is one key contributing factor leading to the existence of complex changes. The last paragraph finally bridges empirical neuroscience with morality in that it outlines the neurophysiological importance of the basal ganglia in our ability to achieve executive control, a key function in the context of moral behaviour.

1.1 Deep Brain stimulation: Procedure

Iconic figures such as WALTER HESS and JEAN SIEGFRIED from Berne and Zurich respectively, represent two prototypes who have been actively involved in DBS development. While JEAN SIEGFRIED treated patients suffering from chronic pain in 1976 with DBS and performed a first intervention for movement disorders in a dyskinesia patient in 1982, WALTER HESS performed experimental brain stimulation in cats already in the 1940's. WALTER HESS, who was later awarded the Nobel Prize in Medicine (1949), was director of the physiological institute of the University of Zurich. Although thalamotomy represented an established target in the treatment of tremor, the idea to use stimulation as a therapeutic modality did not emerge until BENABID's preliminary report in 1987 (Benabid et al., 1987) on stimulation of the Vim (ventral intermediate nucleus of thalamus). BENABID and the Grenoble group including PIERRE POLLAK, who now works in Geneva, pioneered chronic stimulation of the STN for PD and reported their first patient in 1994 based on the findings from animal experimentation (Benabid et al 1994, Pollak et al 1993). Hence, the roots of DBS can be traced back to France and Switzerland.

DBS represents a symptomatic therapy and currently is offered as escalation therapy only. It comprises a high-precision method in which a patient is implanted one or two electrode leads into a specific brain region, usually located in the basal ganglia. Electrodes are inserted into the brain via burr holes in the skull using neuroimaging-guided stereotactic neurosurgery. Leads typically contain several contacts and are connected via a subcutaneously implanted pulse generator (IPG) in the clavicular or abdominal region containing the systems battery and computer that drives stimulation. Despite a lack of proven (patho-)physiological-based evidence, typically used parameters in clinical settings for the treatment of Morbus Parkinson include frequencies of 130 Hz, pulse widths of 60-90 µs and intensities of 1 to 4 Volts. Stimulation of neuronal tissue at any frequency evidently excites various neuronal elements, including (mostly) myelinated axons in vicinity of the electrode. After the induction of an action potential, it may flow in orthodromic and antidromic directions. It is likely that the therapeutic effect has more to do with stimulating the axons than with the stimulation of neurons within the target. Apart from hardware related complications (e.g. lead migration or fracture), risks of this type of intervention (such as infections, haemorrhage) are comparable to other brain surgeries, less risky compared to tumor resections and repeated minor surgery is required for IPG replacement only. In addition, DBS is said to be a reversible and adaptable procedure. The integration of precision medicine of this sort into the therapeutic landscape requires multidisciplinary teams of highly qualified experts.

1.2 Clinical relevance of deep brain stimulation

During the last 25 years, tens of thousands of patients have been treated with DBS (Lozano & Lipsman, 2013) suffering from the most debilitating symptoms of a multitude of disorders. Early lesion studies in humans and laboratory animals aiming at interrupting putative circuits together with stimulation experiments marked the origin for the development of DBS. Since the beginning of the treatment of mainly tremor-dominant Parkinson patients through thalamic high-frequency-stimulation (HFS) till today, knowledge gained from DBS as both a probe and modulator of the underlying neural circuitry resulted in a new way of describing and understanding (neuro)-pathologies. Likewise, the rapid development reached a non-undisputed (Hariz et al., 2013) broadening of therapeutic spectrum ranging from the treatment of neurological disorders, such as chronic pain, epilepsy and movement disorders (mainly essential tremor, dystonia and Parkinson's Disease) to neuropsychiatric disorders, such as obsessive compulsive disorder and depression, to name a few. DBS unquestionably is a remarkable therapy and has been shown to be more effective than best medical treatment for some disorders. Unlike pharmacological treatment, for some patients suffering from different disorders of the brain, the improvement with DBS is present at the click of a switch. The nearly instant improvement of many neurological disorders, for neurologists, provides a gratification not usually afforded in this discipline.

1.3 Prospects of technological deployments

In order to minimize stimulation-induced adverse events (described in „Section II: The ethics of behavioural and affective changes following DBS"), the following future technological advances are under way: First, closed-loop devices are believed to symbolize next-generation DBS devices. They are characterized by their capability to detecting errors through feedback and by automatically adjusting the critical parameters in response to changes in the brain. Hence, they can correct stimulation on their own depending on electrophysiological or neurochemical imbalances (Abbott, 2006; Potter et al., 2014, Rolston et al., 2010). Secondly, the potential of field-steering for shaping the stimulation to target anatomy by overcoming conventional annular DBS electrode configurations provides a promising mean. Generally, two main approaches, both aiming at field steering, are being pursued: (1) segmented DBS electrodes based on mechanically assembled leads and (2) DBS electrode arrays. Finally, and because neurons and glia communicate at a micron to submicron level, the development of (PPy-coated) carbon-nanofiber-electrodes, if achieved in the near or far future, will permit greater sensitivity in recording electrical activity and greater safety, precision and hence efficacy in stimulating brain tissue. Vascular malformations and tumors located very distal to the major arteries of the circle of Willis are nowadays catheterized routinely. Electrodes within blood vessels supplying nervous system tissue can record and stimulate electrical activity as effectively as electrodes in the parenchyma adjacent to the blood vessels (Llinas et al., 2005). The idea of newly fabricated nanofiber-electrodes which have already been tested in vitro and to a minimal extent in vivo, is to enter the brain's capillary system minimally invasively and precise placement of the electrodes (dozens or hundreds, if desired) anywhere in the brain. Because red blood cells have a diameter in the µm-range, it is even possible to enter the parenchyma without the risk of bleeding from capillary wall puncture (Andrews et al., 2012). However, this idea is still largely hypothetical.

1.4 Balancing the brain

After the initial usage of ventriculography 25 years ago with which help one is able to only visualize two landmarks in the three-dimensional brain, the anterior - and posterior commissure, the enormous progress in visualizations provided by MRI techniques together with the development of stereotactic frames (Hariz et al., 2010) paved the way for individualized lead implantation and DBS as a means for modulating the brain.

Over the last three decades, a large number of patients have been helped by DBS, yet a comprehensive scientific understanding of the underlying mechanisms of action is still missing. As a matter of fact, DBS has revealed more about how the brain works than about how DBS works and has proven that current notions of pathophysiology, particularly of basal-ganglia disorders, are simply wrong (Montgomery, 2007): recent studies showing that both pathways, the direct and indirect cortico-basal ganglia pathways which were believed to exert opposing effects, are activated during the initiation of action, the stopping of action and the initiation of a behavioural sequence (Jahanshahi et al., 2015) depart from the linear "push-pull", direct-indirect dichotomy. Also, according to the GPi Rate Theory, overactivity of the GPi is assumed to cause the motor dysfunction of PD and that decreased GPi activity frees ventrolateral thalamic neurons from inhibition generating involuntary movements such as dyskinesia. However, studies show that DBS of the STN and GPi drives GPi activity (Montgomery & Gale, 2008) and that this increased activity facilitates movements in patients with PD. Stimulation of neuronal tissue at any frequency evidently excites various neuronal elements, including (mostly) myelinated axons in vicinity of the electrode. After the induction of an action potential, it may flow in orthodromic and antidromic directions.

Because DBS provides the exceptional opportunity to probe brain function and dysfunction, as evidenced by the previously outlined example of e.g. Montgomery and Gale, it provides a substrate for investigational research by e.g. recording from implanted electrodes. It is possible to record electrophysiological changes (altered firing rates and patterns, pathologic oscillatory activity and increased inter-neuronal synchronization) of neurons in the basal ganglia and related regions in thalamus and cortex by e.g. single-cell recording techniques. Moreover, changes in joint spiking activities at a neural population level can be observed by deploying local field potentials (LFPs), electroencephalograms (EEGs) or electrocorticograms (ECoGs) (Galvan et al., 2015). It can also be coupled with neuroimaging, and genetic profiling studies. Many hypotheses about network dysfunctions contributing to pathological states emerged as a result of such investigations (e.g. increased oscillatory power in the beta frequency band in PD, Hammond et al., 2007). In PD, the loss of diencephalic dopaminergic cells may lead to unbalanced basic oscillations between cortex and subcortical regions. In light of this, DBS serves as an important tool for rebalancing resting state network activity in brain disorders (Kringelbach et al., 2011). Hence, DBS represents an important tool both for alleviating human suffering and for obtaining novel insight into the nature of fundamental brain function.

It has long been a lost notion, that the brain is to a great extent an electric device and as a result has properties uniquely instantiated in the electrical activities distinct from those of neurotransmitters (see L. Galvani, or Giovanni Aldini who published an influential book that reported experiments in which the principles of Luigi Galvani and Alessandro Volta were used together for the first time over 200 years ago). While neuro-(psycho)-pharmacology was and still is a dominant force in the investigation and treatment of brain diseases, the introduction of DBS contributed to the notion that electrophysiology plays a crucial role both for the understanding of the intervention itself, but also for the investigation and characterization of distinct electrophysiological fingerprints of diseases of the brain. As a result, from initial hypotheses stating that e.g. psychiatric disorders are caused by chemical imbalances (e.g. monoamine hypothesis of depression), to more complex theories that involve brain circuit interactions and plasticity, research aimed at unraveling the mysteries of brain disorders and has allowed the development of network models of disease (e.g. Llinas (1999) coined the concept of "network-dysrhythmia" or McIntyre & Hahn, 2010 who highlighted the notion of the interplay of pathological oscillations in a network). In fact, the emphasis on the neuron doctrine introduced by Cajal by emphasizing the individual neuron may have contributed negatively to the exploration of recurrent network models with emergent properties (Yuste, 2015). Still, quantitative outcome metrics and biophysical markers are needed for a better definition and more accurate classification of brain disorders on the basis of their etiological and pathological aspects. As important is the need to carefully document neurobehavioural outcomes.

Undesired behavioural side-effects, in the meantime, are construed as emanating from the complex interplay of drug-reduction, electric current spreading into the neighboring tissue and the progression of the disease. In fact, the often observed sequelae involving apathy, mania, speech problems (among others) may result from not stimulating targeted circuits with the requisite precision, overstimulating them, or from expanding effects to other circuits. Focused stimulation is challenging because many brain functions and the physical and mental capacities they mediate involve distributed and interacting neural pathways that send projections to and receive projections from each other. For example, the subthalamic nucleus in the basal ganglia is one of the areas stimulated to restore motor control in Parkinson's disease (PD). Yet the subthalamic nucleus, and with it the basal ganglia, as will be outlined below in some more detail, consists of a complex network involving not only a motor circuit but also associative and limbic circuits mediating cognitive and emotional processes. For example, the compulsive behaviour of some PD patients receiving DBS may be explained by unintended excitatory effects on the limbic circuit (Castrioto et al., 2014). Particularly the recent notion of re-entrant network loops reflects both the complexity of positively influencing a certain function without influencing yet another function but also shows that theoretically, DBS can modulate output function at any point of the loop. Recent results clearly demonstrate that once believed, highly segregated circuits are in fact interconnected to a higher degree. This is exemplified by referring to the once believed segregation of D1 and D2 medium spiny neurons (MSN) which faded into thin air after demonstrating extensive cross-talk (Calabresi et al., 2014, Kupchik et al., 2015). The D1-D2 distinction refers to the direct and indirect basal ganglia pathway concept (as outlined above). It is believed to adequately describe the promotion and inhibition of movements in a highly segregated fashion and still is the most often used model for (1) describing the emergence of PD, a hypokinetic movement disorder, as well as (2) pinpointing potential therapeutic effects of DBS. Hence, the notion of a modular organization of the brain has probably to be replaced by more recent dynamic network models. According to the modular organization, specific areas in the brain perform specific functions. Although these functions are being integrated to cause a final behaviour, the integration is fragmentary and often sequential. In the meantime, there are other conceptualizations such as the Systems Oscillators theory which appears to be more precise and less contradictory in describing brain function. This theory refers to the brain being composed of sets of loosely coupled interconnected networks of oscillators made up of reentrant activity in closed feedback circuits. After this notion, physiological and behavioural functions are distributed throughout the network rather than restricted to a specific structure that implies a given function. Hence, a desired function can be targeted by DBS anywhere within such a network. In sum, current knowledge rather leads away from one-dimensional, sequential push-pull theories (e.g. of simple over- and underactivity) for the sake of conceptualizations which point at nested or interconnected oscillators representing many different frequencies (Montgomery, 2007).

However, it is important to add that the above delineation which involves the conception of network-diseases bears the danger of exclusively focusing on objective electrophysiological and neurochemical measures of brain activity which may ignore the phenomenological aspect of having a neurological or psychiatric disorder. It is persons rather than neural circuits that have and suffer from diseases of the brain (Glannon & Ineichen, 2016). Thus, the medical, psychological and social needs generated by these diseases are in the sum vital parameters that should be considered at any time of the therapeutic process. To narrow down the network-physiology of disorders of the brain is a necessary but not a sufficient undertaking. What it means to live with a neurological or psychiatric disorder is often expressed by a multitude of other factors including behavioural and affective reactions. Such reactions are a central component of the therapeutic but also the investigational process aiming at explaining a brain disorder.

1.5 The Basal Ganglia: From neuroanatomy to behaviour and affect

As implied previously, the basal ganglia are the primary target for DBS interventions. In what will follow, I briefly outline how the basal ganglia can exert behavioural and affective function.

The basal ganglia are subcortical nuclei consisting of the nucleus caudate, putamen, substantia nigra (SNr and SNc), the subthalamic nucleus, the globus pallidus (GPi and GPe) and the nucleus accumbens together with the greater part of the olfactory tubercle and the rostral part of the substantia innominata (Nieuwenhuys et al., 2007). Besides being connected to motor cortical areas (motor cortex, supplementary motor area (SMA), premotor cortex, cingulate motor area and frontal eye fields), the basal ganglia connect to a lot of non-motor areas of the cortex and subcortical structures, including the superior colliculus, the pedunculo-pontine nucleus (PPN), the periaqueductal or central grey (PAG), the amygdala, the dorsal raphe nuclei, the pontine nuclei and the medullary reticular formation. Traditionally, the basal ganglia have been considered to be important for producing behaviours mainly by their inhibitory action in motor domains. Hence, they are implicated in disorders of movement such as PD, but also in Tourette Syndrom (Ts) or obsessive compulsive disorder (OCD).

However, the role of the basal ganglia has expanded from motor-based conceptualizations to cognitive and emotional domains. The basal ganglia orchestrate output through neuronal inhibition, disinhibition and facilitation, processes that allow flexible interactions and which are the essence of executive control. At least in the classic model, the output nuclei (GPi and SNr) hold the cortex and superior colliculus under tonic inhibition to prevent inappropriate (i.e. maladaptive) movements and can phasically release this inhibitory control to allow movements (Jahanshahi et al., 2015) if MSNs are in the physiological UPSTATE and enough dopamine is present (Da Cunha et al., 2015). Executive control, for example, is important to override habitual or prepotent responses. It constitutes appropriate and context-specific inhibition and facilitation which is relevant to our ability to control our emotions, focus our attention, exert self-control and engage in behavioural regulation necessary for social interaction. Therefore, adaptive behaviour owes as much to taking appropriate action as to inhibiting or suppressing contextually inappropriate or socially unacceptable behaviour. Hence, the basal ganglia are important nuclei in facilitating or inhibiting certain behaviours. Notably, the inhibitory action is difficult to observe and hence perhaps underestimated (Jahanshahi et al., 2015).

Apart from the previously described connections, it is noteworthy to add that the nucleus accumbens (NAc) receives strong dopaminergic inputs from the ventral tegmental area (VTA) and is part of the medial forebrain bundle, a target which is used for the treatment of refractory depression via DBS. The NAc furthermore is well characterized as a hedonic hotspot. Hence, these structures are implicated in motivation and the support of goal-directed behaviours and can trigger addictive behaviours. Secondly, important connections comprise the amygdalostriatal projection (implicated in fear-responses and hence also implicated in MDD) which is distributed to all parts of the caudate-putamen complex and the numerous connections of the basal ganglia with the hippocampus (associated with procedural learning and working memory) and the mesencephalic raphe nuclei (a serotonergic center implicated in MDD).

Parkinson's disease is also a disorder of executive control and DBS mainly targets nuclei in the basal ganglia. Hence, the dysexecutive syndrome which is described as a dysfunction in executive functions such as planning, abstract thinking, flexibility and behavioural control, often manifests in patients suffering from PD. Given the above described influences of the basal ganglia which reach far beyond mere motor control, complex behavioural and personality changes are likely to occur following basal-ganglia-DBS surgery and stimulation.

Lack of context-appropriate inhibitory control leads to impulsivity which includes risk taking, reflection impulsivity and aversion to delayed gratification and is implicated in many neuropsychiatric disorders. Thus, impulsivity can form the basis of one typ of complex behavioural and personality-related changes following DBS interventions. Hence, inhibition (and more specifically proactive as opposed to reactive inhibition) allows for self-regulation of emotion, behaviour and thoughts. Pathological non-motor inhibition, in contrary, is common in attention deficit hyperactivity disorder (ADHD) and OCD. Among others, a range of impulse-control disorders (ICDs) including pathological gambling and hypersexuality have been described as attributable to dopamine agonists in patients suffering from PD. Such behaviours reflect impaired behavioural regulation based on changes in mesolimbic dopamine pathway. Consistent with the proposed role of the STN in inhibitory control, damage to the STN, the most common DBS target for PD patients - through infarction or tumor -, can result in behavioural disinhibitions such as hypersexuality, hyperphagia, logorrhoea and disinhibition of mood, impulsivity and aggression. STN-DBS in some studies resulted in mirthful laughter (Krack et al., 2001), in acute sadness and crying when stimulating a lower contact residing in the SN (Bejjani et al., 1999) or in the onset of new ICDs after surgery (Moum 2012, Lim 2009). However, while DBS can worsen or cause the development of ICDs in some cases, it can also be an effective (indirect) treatment (Broen et al., 2011). In sum, DBS of the basal ganglia in general can produce changes in cognition, emotional state and self-regulation. Such effects are attributable to both failure of inhibition such as impulsive, perseverative or disinhibited behaviours and excessive inhibition. Failure of inhibition include frontal lesions, trichotillomania, mania, Ts, OCD, ICD and hemiballism, chorea and dyskinesias whereas excessive inhibition comprise akinesia (including freezing), abulia and apathy (Jahanshahi et al., 2015).

In fact, executive control (or self-regulation) is an important topic in evolutionary anthropology and also in models trying to describe the genealogy of morality. Apart from the notion that the capability of inhibiting certain instincts might be a true Specificum Humanum, it is adaptive to possess the ability to, in cases of competing goals, not only give room for the stronger instinct but to be able to consider prospect of success and the like. Sometimes, it might be better to wait for a while and to follow another, yet less important goal in the meanwhile. In the tradition of Arnold Gehlen, an important figure in philosophical anthropology, this phenomenon was termed the Hiatus of self-control (Gehlen, 1966, p.35f). Being able to inhibit certain goals for the sake of other executive plans - possibly only experienced in a modus of anticipation -, implies the development of a complex sense of time including anticipation and foresight. In fact, not only future actions have to be anticipated but also the motivational moods and motives which help coordinating the respective action. As a result, executive control can be conceptualized as a defining characteristic of morality. To put aside own desires, particularly if perceiving that intentions and goals of others might be harmed, can symbolize a defining property of morality. Also Wallace (Wallace, 1994) articulated that free autonomous agents must possess the powers of „reflective self-control". This very idea, that autonomous agency involves the capacity to stand back from and evaluate one's first-order desires is widely shared by philosphers of both a Humean and a Kantian cast (e.g. Bratman, 2000 or Kennett, 2001). Finally, self-regulation relates closely to the definition of Moral Intelligence, a psychologically informed framework outlined at the end of part II of this introduction.

In sum, DBS, by interfering with the predominantly inhibitory basal-ganglia action leading to disinhibition of various nodes in the network and by exerting effects on concomitant medication, is thought to exert effects on behaviour and affect which might well extend to a moral domain. It is for this reason that the development of an instrument for measuring moral competencies is decisive (see „C. The problem of conflicitng outcome interpertations following DBS intervention“).

Section II: The ethics of behavioural and affective changes following DBS

SUMMARY:

In the second part of this introduction, I shift the focus to the ethical analysis of complex changes. I argue that the general topic can be framed by a process logic which involves an intervention, potentially leading to complex changes which may lead to conflicting outcome interpretations ultimately leading to suboptimal clinical outcomes. The first construct involves an ethical intervention assessment, which is central to ethics analysis in general and can be structured by incorporating two general principles namely beneficence and non-maleficence. Next, I provide examples of complex behavioural and affective changes and argue that the intervention assessment is non-trivial, as complex changes can result from a potentially ongoing neurodegenerative process, drug reduction, stimulation and their interrelation. The evaluation of complex changes which transcend mere side-effects and hence extend towards a moral domain is likewise non-trivial due to the relativistic nature of morality (i.e. moral jugments often depend on context and time and hence can be framed according to inner-societal disagreement and evaluation instability over time). I next argue that complex changes are especially problematic if undermining the autonomy of the patient. As a result, and when dealing with conflicting outcome interpretations (i.e. between patients, their relatives and clinical experts), a relational understanding of autonomy becomes important. Hence, I discuss the importance of giving the patients and their surroundings the necessary time to prepare for changes that are to be expected within a context of shared-decision making. Given the fact of occurring ICDs post-DBS, the discussion requires an analysis of potentially dysfunctional psychological competences such as abilities relating to moral sensitivity, decision making or behavior, which are hardly the basis of current assessment processes. Hence, after having outlined the promising basis of DBS for efficacy testing as well as the importance of evaluating psychological competences, I argue for the importance of developing psychologically informed instruments in order to measure pre-post DBS effects which are meaningful for patients and their surroundings. The fact that autonomy, besides other abilities, also requires moral competencies stipulates the previously formulated need of new instruments in order to quantify the latter. I refer to a recently developed framework termed Moral Intelligence and end the introduction by attributing explanatory power to our newly built instrument when dealing with conflicting outcome interpretations and the circumscription of complex changes following DBS.

After Henrik Walter, “good philosophy needs a dab of speculation, which, however, should be firmly anchored in historical and empirical knowledge.” He further states that “we can consider neurophilosophy as a discipline that moves in on the mind-brain problem from two opposite directions. Either we begin on the empirical side and happen upon philosophical questions, or we set out with philosophical puzzles and need empirical findings to solve them” (Walter, 2001). Hence, the appropriate strategy is neuroethical research translated, bi-directionally, between empirical (pre)-clinical neuroscientific research and normative philosophical reflection. However, my approach is closer in spirit to the first method Walter describes.

Contrary to empirical research, the thoughtful inquiries into the ethics of neuromodulation represented in numerous publications nicely demonstrate the many areas in which ethical analysis can contribute to clarity of thought – not by removing doubt but by introducing it (Radden, 2004). The following section on normative considerations of the ethics of behavioural and affective changes following DBS interventions is structured along the process logic visualized in Figure 1. It aims at providing a simplified overview of the three main components which will be discussed below.

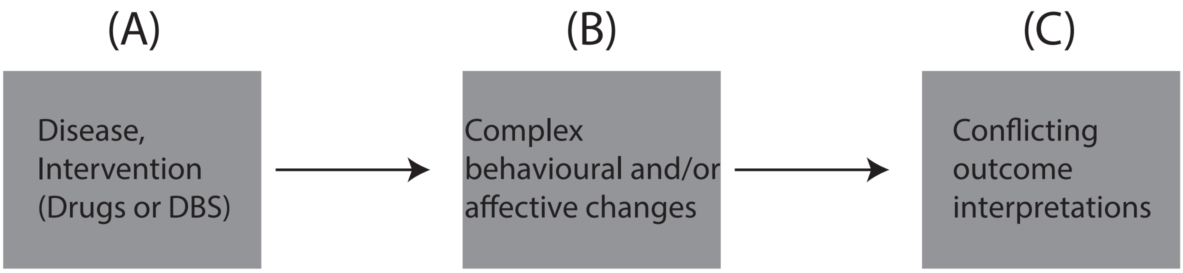

FIG1. Framework for structuring the normative part of this dissertation. Both a disease or any type of intervention targeting the central nervous system (CNS) (A) can lead to complex behavioural and/or affective changes (B) which not rarely are the cause for conflicting outcome interpretations (C) and hence influence the general assessment of the intervention.

After having provided information on component (A) and (B) from an empirical point of view in Part I of this introduction, I shall now proceed to its normative assessment.

A. Intervention-assessment

The evaluation of any type of intervention targeting the human CNS, but also many of the questions which will be addressed in this cumulative dissertation later on, fall within the field of NEUROETHICS (NE). NE can be defined broadly as the study of ethical issues pertinent to knowledge about the central nervous system. It pursues two aims: evaluating the ethical consequences of findings, methodologies and tools used in neuroscience (Part II of this introduction), and analyzing the consequences of knowledge gained in neuroscience on human moral agency to our understanding of ethics (Illes & Raffin, 2002, Roskies, 2002) („1.5 The Basal Ganglia: From neuroanatomy to behaviour and affect“). Hence, the field represents a branch of bioethics concerned with ethical issues arising from investigating, monitoring and modulating the central nervous system. There are many neuroscience-society tension points which foster and justify the relevance of NE (e.g. pharmacological enhancement, lie detection using neuroimaging, use of biomarkers to predict human behaviour or mental disorders, free will and personal responsibility). NE tries to bridge empirical brain sciences, normative ethics, philosophy of mind, law and social sciences.

Generally, the assessment of whether and to what extent the procedures and drugs aiming at helping patients suffering from diseases of the brain can benefit or harm them is a key issue of NE. Actions benefit the patient when they satisfy their interests and they harm patients if they defeat their interests. Hence, assessing the severity of prospective side-effects together with the potential for symptom relief is necessary to evaluate whether a course of action is obligatory, prohibited or permissible. In the context of an intervention-evaluation, the principles of beneficence and non-maleficence are of particular importance and often represent a straight-forward way for assessing whether to endorse a certain treatment strategy or not.

The principle of non-maleficence, one of the two core bioethical principles which can be traced back to the HIPPOCRATIC OATH, refers to PRIMUM NON NOCERE (FIRST, DO NO HARM) and includes the promise to abstain from doing harm, is particularly important in this context. Hence, the topic of dealing with side-effects itself unequivocally represents a source for ethical investigation. The adherence to the principle of non-maleficence first and foremost implies that one is able to assess negative effects. Hence, there is a direct link to the problem of measuring complex unintended effects.

This measurement problem of component B (Fig1) („B. Complex behavioural and affective changes") which complicates the assessment regarding the underlying risk-benefit ratio, will be discussed at the end of this introduction in the context of component C (Fig1) („C. The problem of conflicitng outcome interpertations following DBS intervention") dealing with conflicting outcome interpretations. For now it is enough to say that if one is unable to measure potential changes with the requisite precision, consequently one is unable to decide whether the current practice complies with the general duty of non-maleficence. Additively, this complexity is likely to increase because some side-effects are controversially evaluated by different stakeholders (e.g. patient and his partner) (see component (C), Fig 1 „C. The problem of conflicitng outcome interpertations following DBS intervention").

The duty of beneficence, a second core bioethical principle, could be described as the duty to promote the good of others and reflects a general duty of any medical intervention. This duty must be balanced against the duty of non-maleficence in order to verify whether a positive risk-benefit ratio results. In the context of the principle of beneficence, the following ethical questions emerge: Firstly, and as implied in the first part of this introduction, the feeling of beneficence (e.g. happiness, well-being, absence of pain) has itself a neuronal basis and can be modulated by DBS and or medications (Synofzik et al., 2012). This implies that the assessment of potential beneficial effects of a DBS intervention can become heavily obscured and could point at the need for an a-priory definition and consensus on what "beneficence" means in a particular treatment approach. Secondly and in what will be discussed later, DBS can result in complex behavioural changes (see component (B), Fig 1 „B. Complex behavioural and affective changes") which are evaluated positively by the patient, but which can have consequences on the beneficence of his/her social surrounding.

B. Complex behavioural and affective changes

Characterizing complex behavioural & affective changes

Based on the first part of this introduction, we can summarize the following: Even if not accepting a reductive-materialists theory, most scholars would agree nowadays that the brain plays an exceedingly important role in the formation of who we are as a person. This is not restricted to the notion that the brain holds the capacity to produce a myriad of different behaviours. As a result, it is evident that changes in the brain can result in aberrations of relevant behaviours. Behavioural changes may result from sudden injuries, slowly progressing diseases and some may even result from therapeutic interventions intending to counteract brain disorders.

While some patients show aberrant behaviours due to accidents (e.g. accidents which cause frontal lesions, exemplified by the classic prototype involving the story of Phineas Gage showing a clear relationship between brain and moral behaviour), others may show deviations of what we would consider normal, socially acceptable behaviours because of neurological and psychiatric disorders, like Parkinson's disease or autism spectrum disorder. Novel therapeutic deployments such as deep brain stimulation may represent a way out of such problems but pose themselves the risk of inducing unwanted behavioural side effects (see Fig1).

It is not surprising that it represents a complex task to investigate psychosocial and behavioural consequences of such a complex intervention. From an ethical point of view, the assessment of psychosocial and complex behavioural consequences is an important undertaking when assessing the legitimacy (see „A. Intervention-assessment") of such interventions. Complex behavioural and affective changes can include apathy, hypomania, compulsive behaviours such as gambling and hyper-sexuality, egocentrism, obstinacy, violence, lying or depression apart from other fine-grained changes which may reach far into the domain of personal convictions, values and sensitivities. It has been shown that DBS can result in impatience, irritability, distractibility, attention problems, problems in ordering complex actions and thoughts, anticipation and planning (Müller, 2010) and in premature responding in high conflict situations (Frank et al., 2007). The previously mentioned complex changes have in common that they are characterized by motor and affective components (I deliberately exclude cognitive components because current and past research dealing with side-effects already broadly explored the latter (e.g. language or memory problems)). Whilst the first can include reduced/increased motor drive, the latter can involve anhedonia, depressed mood or increased emotional tone. Such changes are often particularly meaningful for patients and their relatives because they represent defining elements of the treated patients' personality and hence influence social coexistence.

An important difference which is relevant in this context is the distinction between intended and unintended behavioural and affective changes. Contrary to the neurological context, in psychiatry, the mere intention of changing one's "personality" is at the core of the therapeutic aim. Hence, the problem of how to deal with intended as opposed to unintended changes will gain relevance when psychiatric conditions are object of DBS interventions (e.g. who decides which complex changes should occur, how controllable are these, etc.). In what follows, we shall focus on unintended behavioural and affective changes. The primary and direct aim of DBS in the neurological context is to specifically improve agency (i.e. motor or executive control). However, as elaborated in the first part of this introduction, the procedure in general lacks a high level of specificity due to interacting circuitries. Hence, theoretically, DBS might influence agency and "personality" in general relatively unspecifically. In addition, improved motor control (agency) provides access for new opportunities due to regained motor skills and might in turn indirectly influence the psyche of the individual being treated.

Apart from the possible restitution towards a normal psychophysiology, changes in personality traits or behaviour can occur after DBS surgeries both in the adaptation phase (i.e. first 12 months) and in the long-term treatment phase. In cases of undesired, non-inherent disease related changes, stimulation parameters and medication need to be adjusted post-operatively. Behavioural side-effects often reflect a complex interaction between drug and stimulation parameters but changes in general are likely also the result of an ongoing neurodegenerative process e.g. in the context of PD. Also, the reduction of dopaminergic medications after surgery in PD, for example, has been identified as a possible cause for behavioural and affective problems: Forced reduction of dopaminergic medications can lead to apathy and depression. On the other hand, dopamine agonists often cause impulse control disorders and related behavioural disturbances (hypersexuality, pathological gambling, excessive shopping, etc.). Finally, stimulation may induce behavioural changes (see Part I of this introduction). In particular, increased impulsivity by STN-DBS or DA-agnoists may interfere with deliberate actions. Additional contributing factors include lead location, preoperative neuropsychiatric status, postoperative psychosocial (mal)-adaptation and premorbid personality traits. More general adverse effects such as increased tonic muscle contractions (when stimulating the internal capsule) or balance problems when stimulating the brachium conjunctivum also include effects associated with intracranial surgery, such as intracerebral haemorrhage, edema and infection, which are within the range of typical neurosurgical complications. As mentioned, they also include mania (e.g. due to current leakage into the neighboring VTA), depression, apathy and compulsive behaviours such as gambling and hyper-sexuality (Müller & Christen, 2011; Christen et al., 2012). One particular aspect that reaches beyond conventional motor and non-motor aspects of PD and that has received less attention in the context of DBS is moral behaviour (see below). As will be elaborated, problems in social adjustment raise ethical questions that relate to competences and abilities of the patient with ethical relevance (e.g. agency, autonomy, socially acceptable behaviour) and that relate to consent capacity after DBS (Leentjens et al., 2004) and conflicting outcome interpretation due to (e.g.) unmet patient expectations or when the changes are evaluated positively by the patients, but negatively by their social surrounding. Those aspects may require decision procedures in case of social conflicts (Müller & Christen, 2011).

Even though deep brain stimulation seems to favour a hard neuro-essentialist perspective, which refers to reducing behaviour strictly to basic brain processes, subjective reports of motor, cognitive, affective or volitional impairment may be reliable indicators of abnormalities in brain regions at least partially mediating these physical and mental capacities. They unequivocally represent important sources for evaluating the success of a brain intervention. Notable, abnormalities which reflect subtle personality and behavioural changes are often meaningful both for patients and their surroundings. Hence, there is a need to try accurately depicting such changes in such a way that counteracts a too reductionistic understanding but emphasises the holistic nature of complex changes relating to patients and their relatives. Besides that, how a patient reports symptoms, how a clinician responds to the report and how the patient responds in turn to the clinician are fundamental components of the therapeutic process.

In summary, the many contributing factors such as the natural disease progression, changes in medication, socio-economic circumstances and stimulation effects make it difficult to pinpoint causal elements for behavioural and personality-like changes observed after DBS interventions. Given the fact that subtle behavioural and personality-related changes are themselves hard to assess, an ethical discussion of the named changes must lead to a discussion of how to overcome this measurement problem. This will be the topic when discussing conflicting outcome interpretation and the need for new measurements (component (C) „C. The problem of conflicitng outcome interpertations following DBS intervention“). In order to better understand reactive problems after DBS, in-depth psychological assessments of the patients and their surrounding may reveal explanations related to the individual psycho-social situation. In line with the previously said, there is a need to carefully documenting and publishing side-effects that reach beyond simple outcome measures, potentially with the help of new and refined instruments.

Evaluating behavioural & affective changes

Apart from the context dealing with neuro-enhancement or psychiatric conditions, behavioural and affective changes are normally unintended. Such risks are to a greater degree likely to occur in case of neurosurgical or pharmacological interventions targeting the brain.

Medical treatments with the potential of changing the patients' biological foundation of behaviour and affect in such a way that the treated patient may change either abruptly or slowly and as a consequence deals differently with others, warrants additional ethical reflection. Thus, the need for weighting whether possible benefits for patients justify the risk of unintended and undesirable changes in their personality which may negatively affect their surroundings, becomes evident.

Furthermore, the issue relates to the basic problem that there is disagreement on what counts as socially (in)acceptable behaviour. Because morality is often embraced by relativism, moral issues are evaluated controversially and the controversies depend significantly on cultural and societal differences. Additionally, such evaluations may transform over time: First, within a society, there are actions that are undisputedly either moral or immoral, whereas other actions are less clear in that respect (e.g. in respect of (1) murdering innocents or (2) sexual practices such as child-marriage, homosexuality and the like). Second, across societies and during history, the moral condemnation of some behaviours seems to be stable (e.g. murdering innocents), whereas others undergo remarkable changes (e.g. slavery). Thus, moral evaluations of given actions differ both with respect to inner-societal disagreement and evaluation instability over time (Christen & Müller, 2015). For a scientific investigation of brain disorders and their interventions that may cause aberrations of moral behaviour, a universalistic ethical approach would be optimal, because many ethical theories consider universalizability to be a distinguishing feature of moral judgments and a substantive guide to moral obligation: Moral imperatives should be regarded as equally binding on everyone. Additively, ethical theories often regard universalizability as a prerequisite in order that a norm can be called moral. As DBS related side-effects include behaviours for which no universal opinion can be expected (e.g. hypersexuality, evidenced by the high degree of variance of prevalence), the notion of universalizability is fraught with problems. The problem of defining socially (in)acceptable behaviours reaches far into the practice of establishing diagnostic criteria. This is epitomized by the role of values in psychiatry which notions directly enter the definitions of what constitutes a disease within the diagnostic and statistical manual of mental disorders (DSM) prevailing at a given time. Hence, psychiatry ever since adopted the role of making an explicit statement about what morally acceptable ought to be. Otherwise, diagnosis and treatment would be impossible.

Some scholars claim that mental illness is defined by reference to evaluative norms by contrast with physical illness, which is defined as deviation from structural or functional integrity (Thornton, 2007).

As implied previously, it might not even be clear how moral behaviour should be conceptualized. The term moral generally refers to a given set of norms and values which exists in a given society. Consequently, behavioural and affective changes of patients undergoing DBS interventions can, depending on the prevailing context, hold a moral dimension. As a result, the question of which complex behavioural or affective changes have ethical relevance which reach beyond mere side-effects (see principle of non-maleficence), emerges. Ethical relevance is attributable to those changes which implicate moral aspects, that is, changes which hold a social component and/or changes which can conflict with prevailing values or norms existing in a given culture. Such changes include, but are not limited to, changes influencing psychosocial aspects of patients postoperatively and their relation to third parties, behaviours that result e.g. in excessive sexual drive, or changes that might induce harmful consequences for the patients' surrounding. If adopting a broader definition upon which morality is defined by its social component (that is, morality is genuinely social), behavioural and affective changes following DBS modulation nearly always imply a moral dimension because they most often exert consequences on the coexistence of patients and their relatives and society as a whole, e.g. in the form of psychosocial maladjustments (but see „C. The problem of conflicitng outcome interpertations following DBS intervention“, Fig 1, discussed below). Finally, the link between executive control, DBS with its aim to influence it and morality has already been made in the last section of Part I of this introduction.

Why are complex unintended changes problematic?

Brain disorders impose internal constraints on behavioural control (agency) and autonomy. Likewise, unintended effects on behaviour and affect can undermine the autonomy of patients because they relate to competences (e.g. decision making capacity) and the authenticity of patients. Hence, DBS can restore or impair autonomy by e.g. resolving alienation in OCD or by inducing mania in PD. It can also impair the experienced autonomy when patients feel remote-controlled. Autonomy is an important guiding principle in NE because a properly functioning brain is a decisive precondition for being able to act as an autonomous agent. According to Beauchamp and Childress, acting autonomously involves the ability to act 1) intentionally, 2) with understanding and 3) without controlling influences (e.g. coercion or manipulation) (Beauchamp & Childress, 2013). The requirement of absent controlling influences in definitions of autonomy not only includes external manipulation but also internal coercion potentially resulting from a diseased brain, secondary to medications or resulting from a neuromodulation intervention (Müller & Walter, 2010). Any intervention into the central nervous system is commonly evaluated as unethical if it reduces the patient's biological prerequisites of autonomy, when being perform against the patient's will, when causing suffering (see „A. Intervention-assessment“) or when deteriorating the behaviour of the patient in such a way that rights of other persons will be concerned. Importantly, the prerequisites of autonomy include mental capacities but also moral competencies (see „C. The problem of conflicitng outcome interpertations following DBS intervention“).

Regarding the competency component, assessing consent capacity before, during or after DBS interventions is an ethical requirement resulting from respect for autonomy. As a result of pathological brain conditions, it is often unclear to what extent a patient is able to provide informed consent for a treatment which intends to change this condition. It is in the nature of things that this problem extends to interventions in psychiatry, where patients often lack such competencies and where the mere intention of changing one's "personality" is at the core of the therapeutic aim.

In order to uphold the key derivative ethical aim originating from respect for autonomy, namely the notion that the patient's perspective is fundamental, advance directives should be in place to manage states of temporarily losing the decisional competence (Müller & Christen, 2011) e.g. in the case of stimulation-induces mania. If the patient is judgmentally able (i.e. demonstrates decision making capacity), physicians would face legal problems if thinking of discontinuing therapy. In such cases, a contract between patient and physicians might be a good solution.

C. The problem of conflicitng outcome interpertations following DBS intervention

Towards a relational understanding of autonomy

DBS interventions may in some cases lead to complex behavioural and personality-related changes also in the context of movement disorders (as a side-note, PD is nowadays conceptualized as a neuropsychiatric disorder). An additive problem associated with respect for autonomy (see previous paragraph on consent capacity) is the ethical relevance and practical handling of conflicting outcome interpretations between different stakeholders (e.g. patient, relatives, medical experts) with respect to changes in moral/social behaviour of the patient. Hence, the term relational autonomy has been coined to emphasis the notion of a "relational" understanding of autonomy, arguing that decision making should consider not only the individual perspectives of patients, but also those of their families and members of the health care team as well as the perspectives that emerge from their interactions (Epstein & Street, 2011). Such a relational understanding attempts to explain both the positive and negative implications of social relationships for individuals' autonomy, de-emphasizes independence while emphasizing trust and facilitates well-nuanced distinctions between forms of clinical communication that support and that undermine patients' autonomy. In this context, the concept of SHARED MINDS (Epstein & Street, 2011) has been articulated in order to investigate when, why and how individuals involve trusted others in sharing information, deliberation, and decision-making through the sharing of thoughts, feelings, perceptions, meanings, and intentions among two or more people. Resulting from conflicting outcome interpretations, the phenomenon of a satisfaction gap (i.e., disagreement between physicians and patients relating to the treatment success) – potentially secondary to an expectation mismatch, prevailing motor function problems despite DBS intervention, apathy and speech problems and personality changes, among others – is not uncommon in treated patients. The often observed satisfaction gap may also point towards an insufficient sensitivity for complex side-effects (for which no measurements exist) on the part of medical professionals and misconceptions of the patients regarding their pre-operative state.

Because of these difficulties, patients qualifying for DBS are confronted with a very difficult decision of weighing benefits and risks of the intervention against other alternatives. The difficulty is great because of an underlying measurement problem (i.e. the frequency of complex side effects is difficult to estimate) and an evaluation problem (i.e. the retrospective assessment can significantly differ between patients, their relatives and physicians). Psychosocial problems postoperatively emerge either because the patients gained autonomy and rejected their spouses whereas the spouse did not want to quit her role of a caregiver or because the spouses expected more personal responsibility of the patients, whereas those did not want to quit their role as sick persons and demonstate severe problems in proving themselves in the world of healthy persons (i.e. BURDEN OF NORMALITY problem) (Gilbert, 2012, Wilson et al., 2001). Sometimes, postoperative improvements are objectively not optimal and sometimes, there is the problem of satisfaction gaps. Hence, there is a need to transparently inform patients about those difficulties and to include patients, their families and caregivers into the decision making process long before surgery is performed. Numerous causes might exert difficulties in social adjustment such as the adjustment to the new self with a brain pace-maker and suddenly radically improved motor signs, the adjustment to an abruptly changed situation with the significant other and close family whose roles as a caregiver may suddenly change or the adjustment to a new situation at work and with leisure activities. As a result, it is important to give patients and their surroundings the necessary time to prepare for the changes that are to be expected in their lives and as a result to include patients and their relatives early into the shared decision making process (Schüpbach & Agid, 2008).

The importance of psychological competencies and their assessment

The process of shared decision making however, additively requires a discussion of morally relevant behaviours (such as ICDs) which themselves depend on psychological competencies. The underlying psychological competences which might be dysfunctional after complex affective changes however, are hardly the basis of the current assessment process. In turn, new instruments that are able to quantify and depict such competencies might be highly relevant for an improved (i.e. updated) shared decision making. Such a particular psychological competency is moral sensitivity, the ability to recognize morally salient aspects in a given situation. Out of theoretical consideration, it might be possible that DBS constrains the sensitivity of an individual in such a way, that makes it impossible for the patient to recognize that a given person might be harmed by certain actions, even though he is generally of the opinion that one should abstain from harming others. The inability to implicitly recognize the harming nature of certain action following DBS intervention could symbolize a basis for explaining complex behavioural and affective changes. Notably, there is a difference between the inability to subconsciously recognize that a given value might be harmed and the deliberate convictions somebody holds. It is such subtle changes in psychological competencies which soak through the clumsy neuro-psychological assessments which are being used nowadays. Hence, conflicting outcome interpretations emphasize the need for trying out new avenues aiming at thoroughly uncovering more subtle changes following diseases, medication and or DBS intervention.

As outlined, currently there is a lack of sensitive instruments which adequately depict such changes. Standardized questionnaires and tests are available, but they may not reflect sufficiently the behavioural changes and their effects in real life. New avenues for the better circumscription of behavioural and affective changes which may explain causal elements for the emergence of conflicting outcome interpretations may involve instruments which rely on newer insights of moral psychology. Hence and in the following, I outline why DBS is suitable for investigating behavioural and affective changes, followed by discussing the methodological problems of trying to assess complex changes. Finally I emphasize the role of moral psychology and its potential for developing suitable instruments.

DBS as a suitable means for investigating behavioural and affective changes

DBS is suitable for efficacy testing in randomized, double-blind, controlled trials and partially the testing of acute effects (by switching the device on and off). It is even possible to perform sham-stimulations in order to measure placebo effects. Apart from a purely scientific demand, it additively represents an ethical requirement to optimize study designs in order to capture objective therapeutic effects. However, statistically significant efficacy represented in the very abstract improvement captured by rating scale scores is only a necessary but not a sufficient condition. Hence, the quality of life of patients independent of motor functions comprising e.g. psychosocial factors has long been overlooked. Psychosocial maladjustment in this context can be expected after rapid symptom modification in any chronic life-determining disease. Quantitative outcome measures have to be complemented by either qualitative measures or by psychologically informed innovative instruments. As outlined previously, any causal factor (e.g. stimulation, drugs, disease and their interplay) leading to unintended side-effects is by nature non-trivial to identify. Therefore, highly individualized approaches are needed. It is important to note that even though DBS is said to be reversible, non-efficacy results in severe despair in a multitude of patients which strongly depends on the medical care team (Synofzik & Schlaepfer, 2011).

Methodological problems of trying to assess complex changes

As outlined in paragraph A (Intervention-assessment), unintended side-effects represent important ethical factors for the evaluation of novel therapies in general. However, the ethical evaluation of side-effects is associated with two fundamental methodological problems: First, some side-effects are difficult to measure and to quantify exacerbating the assessment of the incidence of certain side-effects. Second, the impact of some side-effects on the patient's life is difficult to classify, especially in comparison with the impact of the diseases' natural progression. Hence, assessing the severity in order to evaluate whether a course of action is obligatory, prohibited or permissible in some cases is very difficult. As a result, any novel therapy is confronted with a measurement problem of this sort. In order to shape the ethical analysis, Müller & Christen (2011) have introduced an analytic scheme that classifies therapy side effects along two gradual, qualitatively described dimensions (measurement complexity of side-effect vs relative life impact of the side-effect weighted by its incidence in the natural disease history). It implies a higher ethical sensibility for complex side effects but also, by incorporating the "relative life impact", accounts for the consequences of not intervening apart from the fact that side-effects are genuinely ethically relevant. The scheme should not be misunderstood as an objective and general classification of the salience of side-effects because whether certain side-effects can be tolerated, compensated for or cause suffering depends strongly on the individual patients' attitudes and life situation (social situation, professional activity, psychological condition, among others). The fact that several effects with small life impact may cumulate to an effect with a high life impact further highlights the importance of individually attributing life-impact scores. Thus, the scheme might serve as a tool in the patient briefing and in shared-decision making.

As a site note and with regard to psychiatric disorders and the involved harm-benefit assessments, numerous core problems arise. Among others, objectively evaluating beneficial or negative effects of the therapy depends more strongly on subjective evaluations. Also, cases with predictable side effects that clearly outbalance therapeutic effects are probably rather rare in this context. If DBS will play an important role in psychiatry, we certainly cannot expect that the side-effects spectrum will become smaller compared to that implicated by the alternatives.

The role of moral psychology and its potential for developing suitable instruments

As outlined above, DBS aims at modulating a complex system which effects are not always foreseeable and which can extend into the social or moral context. Morality can be defined very broadly as a set of norms, principles, values and virtues that are governed by an orientation towards the good. It reflects respect and concern for oneself and other entities (persons, animals, environment). Additively, it is embedded in a justification structure. It is this sort of complex behavioural changes, including social and moral aspects, which are to a greater degree ethically problematic and for which assessment, psychologically informed instruments are highly needed. The field with the richest knowledge on how agents reason, decide and act morally is still moral psychology. In the following, the framework termed moral intelligence (MI) (Tanner & Christen, 2014) might represent an appropriate mean for investigating psychological competencies that may relate to a revised shared decision making. MI is defined as the capability to process moral information and to manage self-regulation, a key-feature already outlined above (see paragraph: the basal ganglia: from neuroanatomy to behaviour), in any way that desirable moral ends can be attained. It refers to the set of skills that moral agents need in order to align their behaviour with the moral ends they have set for themselves, using the broad understanding of "morality" defined above. Hence, this approach emphasizes psychological skills which are important to constitute moral behaviour. MI is composed of five key elements: a moral compass, i.e. a set of moral schemata whose content is responsible for orienting the subject's behaviour (Narvaez & Lapsley, 2005), moral commitment, as the ability to activate and or sustain motivation for the inclusion of moral considerations in the process of perception, decision-making and action, moral sensibility, as the ability to recognize morally salient aspects in a given situation, moral problem solving as the ability to bring morally salient features to the decision making process and to arrive at a decision consistent with the subjects' moral compass and finally moral resoluteness as the ability to carry out own decisions despite of barriers.

In the context of this dissertation, one aim was to operationalize moral sensibility in order that it can be measured. Hence, after having successfully developed the instrument, a major future step will involve the translation of this tool for the clinical landscape in order to investigate subtle changes in patients' sensitivities regarding different moral and non-moral values. The inclusion of an instrument of this sort might enable us to deeper investigate complex changes after DBS interventions. It is thereby most likely, that different neural systems are mediating sensitivities related to e.g. harm versus honesty in a distinctly different way and that the underlying neural mediators may be entirely different. A specific disease may thus impair one aspect of moral sensibility stronger than others but the relevance of this difference will depend on the situation in which this competence is needed. Moreover, a neurological or psychiatric disorder is likely to influence other competencies (also non-moral ones) as many regions in the brain have multimodal and re-entrant functions.

Because it is neither useful for a healthcare professional who is interested in investigating moral behaviour to work with a very broad concept of moral behaviour (e.g. moral behaviour itself) nor with a highly complex and fine-grained understanding of moral behaviour (e.g. impairment of honesty-related moral resoluteness), the need for developing instruments achieving a reasonable compromise is utterly important. Hence, the aim is to have an instrument at ones' disposal which includes a sufficiently but not too complex set of constructs that describe competencies relevant for moral behaviour (such as the MI model). Correlational studies which include lead-position variations in different neuroanatomical targets, increased knowledge about the brains' network architecture combined with psychological data on value sensitivity might therefore turn out to be fruitful for more thoroughly investigate the mechanisms of complex changes.

After having outlined the centrality of psychological competencies required that desirable moral ends can be attained, we are now able to circumscribe such competencies in relation to the previously described concept of „self-control" (see last part of part I of this introduction). In order to act in reference to values and norms, the individual must possess moral concepts and have the capacity to recognize and apply moral reasons appropriately in his practical deliberation. Secondly, such an individual must be able to control her behaviour in accordance with these same reasons. It is quite likely that such capacities come in degrees. While most persons suffering from a psychiatric illness will have acquired ordinary moral concepts, disordered thinking, delusions, depressed mood but also drugs and other medical interventions may reduce or remove the ability to recognize or weigh relevant moral considerations and to judge accordingly.

The role of an instrument measuring moral sensitivity in clinical practice

Finally, I will briefly outline the role of an instrument measuring moral sensitivity in clinical practice. Generally, the deployment of an instrument of this sort is conceivable for the referral practice in DBS interventions and as an outcome-measure in order to measure pre-post DBS effects. Concerning the deployment in referral practice, it is important to examine whether moral sensitivity (MS) represents a defining competency in sustaining primary competencies such as decision making capacity. If MS demonstrated to preserve or substantiate one's ability to act independently, with (self)-understanding and authenticity, then it would only be logical to include the instrument in referral practice in order to have a decisional grounding to potentially exclude patients from such interventions. If MS demonstrated to be decoupled from such abilities, it might be less pressing to include it in the referral process. This however would presuppose having a keen idea how DBS might affect MS which relates to the question whether it should be used as an outcome-measure (see below). Also, the acknowledgment of MS as a primarily relevant competency might shift the general risk-benefit assessment in direction of preservation of MS. Finally, both the potential inability to pinpoint causative factors reducing MS and given the fact that MS is conceived as a competency which can be trained, the specific handling of this construct seems challenging.

Concerning the deployment of the instrument in the outcome-assessment, one would be very tempted to make use of it. For the investigation of meaningful pre-post effects following DBS is an important undertaking, investigating changes in MS would be necessary in order to not only assess the legitimacy of this intervention but also contributing factors which might explain complex changes and conflicting outcome interpretations. Based on the direction of test-results, either a revision of stimulus parameters and/or electrode location (in case of marked changes), or in-depth validation on the sensitivity of the instrument at stake would be needed. Alternatively, DBS might not interfere with MS and the underlying competencies.

It might be a good strategy to slowly approach these questions by e.g. investiaing pre-post effects relating to MS before the evaluation of whether the outcomes may have an impact on referral practice and the content alignment of exclusion criteria.

As I have outlined previously, the perspective of the individual patient is fundamental. Hence, I end the second part of this introduction with an emphasis on the individual patient. The care of patients suffering from severe neurological or psychiatric disorders is often challenging. Based on the previously outlined problem of psychosocial changes, disabilities that directly affect social interactions with others pose challenges to family and caregivers to a greater extent than purely physical disabilities. The challenge is even greater if patients demonstrate questionable moral behaviours (e.g. egocentrism, obstinacy) or even immoral behaviours (e.g. violence, lying). In most cases, people suffering from a neuropsychiatric disorder are not responsible for their diseases. However, they are significantly disadvantaged and suffer from stigmatization apart from their disease. Hence, it represents a moral duty to support them medically but also their reintegration. If the neuromodulatory therapy shows the need for balancing between therapeutic and unwanted effects and indicates that the optimal balancing can look differently depending on different perspectives (patient, close relatives, medical experts), the ethical assessment is even more complex.

In summary, when examining ethical questions dealing with behavioural and affective changes following DBS, difficult "measurement problems" have to be resolved. In fact, standardized questionnaires may not sufficiently reflect behavioural changes and their effects in real life. Hence, there is a need for developing new instruments which are able to enrich the behavioural and affective assessment in order to uncover changes that are meaningful for patients, their surroundings and society. Such changes likely encompass alterations which hold a moral component. As a result, implementing recent insights of moral psychological research in the development process of new instruments is likely to represent a promising solution.

Approaching the research question of investigating clinical and ethical aspects of complex behavioural and affective changes following DBS interventions

The strategy for approaching the research question incorporating clinical and ethical aspects of complex behavioural and affective changes after DBS, including the intervention (DBS) and the targeted diseases (component A), complex behavioural and affective changes (component B), as well as conflicting outcome interpretations (component C), included:

1. First, a quantitative understanding of the field of DBS including clinical and ethical aspects. Hence, we performed a statistics driven approach implementing a network analysis in order to gain an overview of primarily patient relevant issues (such as most often discussed side-effects, anatomical targets and indications) in DBS publications since 1992.
2. Next, an increased understanding of the prevailing global practices based on expert evaluations with an emphasis on patient relevant parameters was approached (e.g. finding elements which might be causative for conflicting outcome interpretations, fears of patients and their likelihood estimation, estimating the occurrence of complex changes in behaviour, among others).
3. Moreover, and in appreciation of the technological influences on the likely emergence of personality-related changes following DBS together with the decisional power the device industry has, we critically scrutinized the technological status quo as a means for an ethical evaluation of important aspects of the technology-development.
4. Finally, and after gaining important insights into the interplay of the device-disease-drug and complex changes-relation as well as the need for new and better instruments for measuring such changes, we developed a psychologically informed instrument which might prove valuable in the context of assessing complex behavioural and affective changes.

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Part II Research

Publication 1: Mapping the field through a quantitative understanding

Synopsis

Taking advantage of recent developments in network analysis, statistics of interconnections and graph theory, we analysed abstracts of 7000 deep-brain-stimulation-papers published between 1991 and 2014. With an emphasis on patient relevant categories such as DBS indications, anatomical targets and side-effects, we confirmed known trends e.g. regarding the emergence of psychiatric indications. As outlined in the introduction, the emergence of both neurological and psychiatric disorders stipulates the need for adequate pre-post assessments with an emphasis on behavioural and personality changes.

The data also reflect an increased discussion of complex issues such as the topic "personality" which is connected tightly to the topic "ethics". In addition, a mismatch concerning an apparently increased interest in depression as an important indication and an unsatisfactorily low description of side-effects was evident. Hence, we outlined the need for the accurate and careful observation and measure of psychosocial and personality-related changes which is backed by our data analysis. We argued that in order to minimize problematic behavioural and personality-related side-effects, DBS should get more individually tailored. In this context, we also advocated for the eagerness to evaluate results beyond short-term quality of life.

Finally, we found a robust connection between hardware-related issues and an ethical context.

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ORIGINAL RESEARCH
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Analyzing 7000 texts on deep brain stimulation: what do they tell us?

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The enormous increase in numbers of scientific publications in the last decades requires quantitative methods for obtaining a better understanding of topics and developments in various fields. In this exploratory study, we investigate the emergence, trends, and connections of topics within the whole text corpus of the deep brain stimulation (DBS) literature based on more than 7000 papers (title and abstracts) published between 1991 to 2014 using a network approach. Taking the co-occurrence of basic terms that represent important topics within DBS as starting point, we outline the statistics of interconnections between DBS indications, anatomical targets, positive, and negative effects, as well as methodological, technological, and economic issues. This quantitative approach confirms known trends within the literature (e.g., regarding the emergence of psychiatric indications). The data also reflect an increased discussion about complex issues such as personality connected tightly to the ethical context, as well as an apparent focus on depression as important DBS indication, where the co-occurrence of terms related to negative effects is low both for the indication as well as the related anatomical targets. We also discuss consequences of the analysis from a bioethical perspective, i.e., how such a quantitative analysis could uncover hidden subject matters that have ethical relevance. For example, we find that hardware-related issues in DBS are far more robustly connected to an ethical context compared to impulsivity, concrete side-effects or death/suicide. Our contribution also outlines the methodology of quantitative text analysis that combines statistical approaches with expert knowledge. It thus serves as an example how innovative quantitative tools can be made useful for gaining a better understanding in the field of DBS.

Keywords: deep brain stimulation, text analysis, network analysis, co-occurrence of terms, bibliometrics, bioethics

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INTRODUCTION

A characteristic of modern knowledge production is the enormous increase of the number of scientific publications (original papers, reviews, conference abstracts, editorial material, etc.) that is made accessible through digital technology. In neuroscience alone, it is estimated that more than 100,000 papers a year are added to a text corpus that contains many millions of publications (Grillner, 2014). This information overload poses a substantial challenge for researchers to keep pace with the developments in their own fields; and it is well-known that the biomedical sciences are especially vulnerable in this regard, since they are strongly oriented toward text-based knowledge sources (Hölzer et al., 2006). This problem certainly also holds within the field of Deep Brain Stimulation (DBS) (Hariz et al., 2013), that has experienced a substantial growth of publications since the late 1990s (Müller and Christen, 2011). In this paper we propose a way to handle this challenge by using quantitative text analysis that combines statistical approaches with expert knowledge.

Quantitative approaches using bibliometrics, scientometrics, and text mining have gained popularity, as they may serve as navigational prospects and orientation aids. They enable researchers to identify relevant topics, trends, and publications in a fast-growing text corpus. Among other methods, network approaches, and data visualization techniques that aim to identify connections between topics within a given text corpus are being used (Popping, 2000, 2003; Ryan, 2007) and have shown to be useful to grasp important concepts within a text of any length. While being applied in a wide field, such approaches have a long tradition in enabling researchers exploring possible configurations of the unknown, shared visual representations which may open new ways for channeling collective attention, envisaging innovative interpretations and help us to make sense of data at different scales (Okada et al., 2014). The ultimate advantage of network analyses and their visual representation in general is recognized from a wide and diverse field. Ideally, the results of such a methodological approach will verify conjectured trends within the field, enrich the discourse, and support unconventional ideas or interpretations of the ongoing scientific development. In the following, we will explore the techniques of sized graphs in combination with sophisticated text preprocessing in order to find features in the network structure of the DBS text corpus which otherwise would be difficult to detect.

In general, a graph visualizes relations of a given set of data and is composed of nodes and edges. Nodes typically represent items or concepts whereas edges connect nodes according to some association rules. Graphs are widely used for e.g., analyzing social networks where people represent the nodes and edges represent relationships between people. To convert information (e.g., of text) into a visual representation can facilitate the handling and perception of hidden structures from large data sets. By following paths and detecting clusters of closely related nodes, one may detect unique features of a given data set. However, if the data set exceeds a certain level of magnitude, the task of exploring, and navigating becomes increasingly difficult. More specifically, there is extensive work on representing textual data as graphs and the subsequent application of network text analysis (e.g., Losiewicz et al., 2000; Grbic et al., 2013; James et al., 2013; Guan et al., 2014) for gaining an increased understanding of influential concepts, text's meanings, and structure. Network analysis is therefore also suitable for linguistic comparative analyses which focus on semantic relations between words, often framed through the co-occurrence of terms (i.e., relevant terms that more often appear in the same text are more likely to share some semantic connection). By making use of the large number of published DBS papers as well as a statistics driven quantitative approach, a potential subjective bias may be diminished.

In the following, we will use graph analysis and visualization techniques for investigating (1) most influential topics, (2) their mutual connections as well as (3) the temporal development of topics by retrieving the titles and abstracts of all published publications from 1991 to 2014 in the field of DBS (see Material and Methods for more specific information). We expect to be able to reproduce known phenomena (e.g., an increase in discussing psychiatric disorders in the DBS literature, well-described anatomical targets for the treatment of various disorders, or known treatment methods for various disorders) which might become obvious in different ways (e.g., direct connections or by reference to how e.g., anatomical targets are being discussed). Additively, we are interested in detecting how specific topics (e.g., lesioning-methods, personality, and bioethics) develop over time and/or how they interrelate with other topics. The original text corpus was composed of more than 10,000 DBS publications, based on which 7154 texts (titles and abstracts) containing more than 400,000 potentially relevant words have been selected for analysis. Using the co-occurrence of key terms as association rule, we conducted graph visualization techniques, community analyses and quantitative metrics to get insight into how DBS has been discussed during the last 23 years.

The results of this analysis are then reflected by referring to issues that dominated the DBS literature. Beside others, we are interested in how some topics that have been identified as ethical focal points in the international practice of DBS (Christen et al., 2014) are represented in this quantitative approach. In this way we explore the potential of such quantitative approaches for identifying subject matters that are of relevance from a bioethical perspective. The study will conclude by a discussion of limitations of quantitative approaches as heuristics to deal with information overload.

MATERIAL AND METHODS

Textual data is complex due to syntactic (verb forms, declination, etc.), semantic (homonymy, synonymy, etc.) and pragmatic (context-dependency etc.) variation. Therefore, any quantitative analysis based on textual data has to ensure appropriate preprocessing of text data such that it can be correctly used for statistical processing. In the following, we first describe text preprocessing to generate the final word set that was then used for trend and co-occurrence analysis, before we outline the network analysis and visualization methodology. The aim of the study was to obtain a comprehensive set of DBS publications as a set for quantitative analysis. We restricted ourselves to papers published since 1991, as earlier papers on DBS are rather sparse and do not yet contain in all cases the string "deep brain stimulation" as a simple identifier for a text that can be attributed to the DBS text corpus.

Abbreviations: ALIC, Anterior limb of internal capsule; BC, Betweenness Centrality; DBS, Deep Brain Stimulation; ECT, Electro-convulsive therapy; ET, Essential tremor; GP, Globus pallidus; GPi, Globus pallidus internal segment; MDD, Major depressive disorder; STN, Nucleus subthalamicus; Nacc, Nucleus accumbens; OCD, Obsessive-compulsive disorder; PD, Parkinson's disease; PPN, Pedunculo-pontine nucleus; QoL, Quality of life; SCS, Spinal cord stimulation; SG, Subgenual cingulate; TS, Tourette syndrome; tDCS, Transcranial direct current stimulation; VNS, Vagus nerve stimulation; Vim, Ventral intermediate nucleus; Zi, Zona incerta.

Text Preprocessing

Text preprocessing contained three steps as outlined in **Figure 1**. The starting point was a search in the Web of Science Core Collection database (the search was performed on December 5th 2014)[1]. We used the search string "deep brain stimulation" in the "topics"-field, restricted to the time range 1991 to 2015. We excluded the "Proceedings Citation Index," because entries in this database only contain the title of contributions without abstract. This resulted in a set of more than 10,000 contributions and a text corpus of almost 1.2 million words. In a first preprocessing step, we deleted special characters (e.g., "(" or "?" including number signs) as well as the search string itself (because it is unspecific), we transformed all letters into lower case and we merged frequent word pairs (e.g., "informed consent" to "informedconsent"). This last step was based on a word-pair statistics over the whole text set to identify very frequent pairing of words (a cutoff value of about 80% was chosen). We identified frequent word pairs by selectively looking through potential word-pairs and decided whether they should be merged based on our experience with the DBS vocabulary (in total, 130 word pairs were merged).

In a second preprocessing step, we deleted standard stop words[2] like "the," "is" etc., and we performed a lemmatization, i.e., we transformed all nouns, verbs, and adjectives into their ground form using standard lookup tables[3]; for example the plural "brains" is replaced by "brain" or the past tense "came" is replaced by "come"—the latter step served for removing the amount of variability. We refrained from stemming (another standard procedure in text processing), because a stemmer operates on a single word without knowledge of the context, and therefore cannot discriminate between words which have different meanings depending on the text. Finally, we computed the text length distribution and we deleted all short texts[4]. The remaining text corpus consisted of 7154 texts and 597,474 words, 22,034 of which were distinct words.

Finally, a third preprocessing step was necessary due to area-specific stop-words and terms that were not contained in standard lemmatizing lists. We first deleted all words that were present in less than 0.1% of the texts (i.e., that are contained in maximal seven texts), because these rare words are not suitable for statistical text analysis. Then, two raters (the authors) independently assessed which words are considered to be unspecific. If both raters independently rated the same words as unspecific, they were deleted (1308 in total). In a similar way, we identified 1380 replacement-pairs for area-specific lemmatization[5]. In this way, we generated a set of 7154 texts that

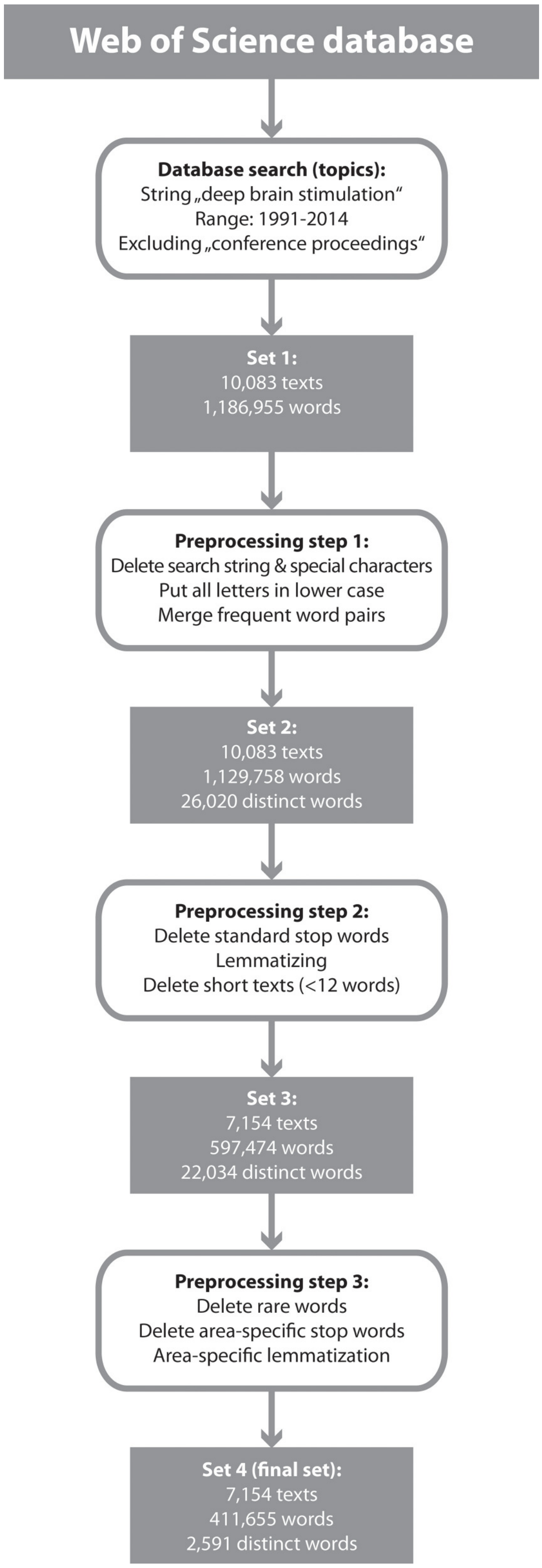

FIGURE 1 | Scheme outlining the generation of the final text set for network analysis.

[1] WoS, Thomson Reuters, access through https://webofknowledge.com/

[2] Available at: https://code.google.com/p/stop-words/

[3] Available at: http://www.lexiconista.com/datasets/lemmatization/

[4] The text length distribution displayed a peak for very short texts (e.g., editorial material that is only present in the WoS database with its title). In the mean, there were 36 texts per bin, the standard deviation was 57. Thus, the distribution was cut where there were more than $36 + 57 = 93$ texts per bin, which was the case for texts that contained 11 or less words).

[5] In some cases, we also replaced verbs or adjectives with nouns; e.g., "painful" was replaced with "pain," because the number of words of one category was considerably lower compared to the number of words of the other category.

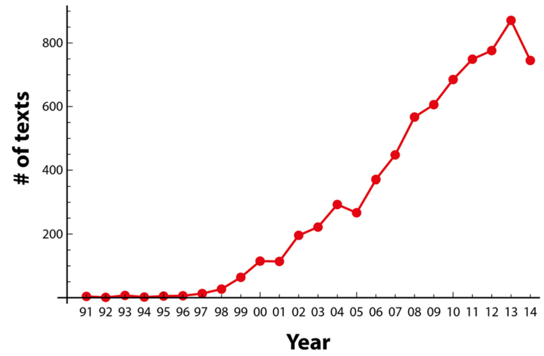

FIGURE 2 | Distribution of publication years of all texts of the final set (7154 texts), indicating a steep growth in the number of DBS texts since the late 1990s.

consisted of 411,655 words, consisting of 2591 distinct words. This set was used for the quantitative analysis.

Figure 2 provides an overview of the text corpus in terms of publication years which shows the quantitative basis for our analysis and reflects the substantial growth of publication within the field of DBS. Text size distribution and term frequency are shown in Supplementary Figure 1.

Text Analysis

The text analysis consisted of an expert evaluation part and a statistical part. The expert evaluation (performed by the authors) aimed to identify terms that are characteristic for issues and topics that are widely discussed in the field of DBS. For issue identification, we also referred to earlier publications from us, i.e., we included issues and topics which were identified as relevant based on an analysis of DBS conference contributions (Christen and Müller, 2011) and a large review covering the literature on DBS in the Nucleus subthalamicus (Christen et al., 2012). "Issues" refer to overarching themes (such as anatomical localization), "topics" refer to defined subject matters within an issue (such as specified anatomical localizations), and "terms" refer to the actual words that appear in the text. As outlined in **Table 1**, seven issues containing 73 topics were chosen for further analysis, based on the authors estimation of relevance (some topics could be in more than one issue; e.g., pain as indication or side-effect). Topics sometimes are composed of different terms (e.g., "accumbens" and "nucleusaccumbens"). In that case, the terms describe the same topic.

In addition, we analyzed ethical issues as a single topic characterized by the terms "ethic," "moral" and "social" because we were interested in investigating on how ethical aspects are being discussed in the literature. In total, we had 74 topics and 162 terms. For these topics, we performed a trend analysis, i.e., we counted the appearance of terms belonging to different topics in all texts of a single year starting from 2000 (due to the low number of texts in the 1990s that contained topic terms). We always normalized the trend data with the total number of publications per year for detecting trends within the whole DBS publication body.

Furthermore, we calculated the pairwise *co-occurrence* $C(X, Y)$ of two topics X and Y as:

$$C(X, Y) = \frac{\left|T(X, Y)\right|}{\min(\{|X|, |Y|\})}$$

Where $\left|T(X, Y)\right|$ denotes, how often the terms characteristic for topic X and Y appear in the same text and $|X|$ respectively $|Y|$ denotes, in how many texts these terms appear in the whole set. $C(X, Y)$ is between 0 (the terms of two topics never occur in a same text) and 1 (the terms always occur in same texts). The co-occurrence is used as similarity metrics for the network analysis.

For visualizing the co-occurrence matrix, we used Gephi, an open source software for analyzing graphs and networks[6]. In the resulting graph, the thickness of the edges reflects the co-occurrence, i.e., a higher probability that two terms appear in the same text is reflected by a thicker and more saturated connection.

The sizes of the nodes (= topics) reflect their betweenness centrality (BC), which is equal to the number of shortest paths from all vertices to all others that pass through that node. The betweenness centrality $BC(X)$ of topic X is defined as:

$$BC(X) = \sum_{X \neq Y \neq Z} \frac{\sigma_{Y,Z}(X)}{\sigma_{Y,Z}}$$

Where $\sigma_{Y,Z}$ is the number of shortest paths between topics Y and Z, and $\sigma_{Y,Z}(X)$ is the number of shortest path between those two topics that pass through X. For example, if there are three different shortest paths between two nodes and a third node is part of two of them, then the BC of this third node and for this specific configuration is 2/3. As a result, nodes with higher BC are more influential, because they functions as junctions for "communication" within the network (Freeman, 1977; Brandes, 2001). Terms with high BC are therefore hypothesized to play the most important role in establishing the meaning for the text and its interpretation.

We visualized the whole network of all topics as well as the networks that only contained topics of two issue classes (we performed six specific visualizations in total: anatomical targets-indication, indication-side effects, anatomical targets-side effects, technological issues-indication, economic issues-indications, positive-effects-anatomical targets. In the following, we display the three of them that yielded the most interesting results.

In some cases, we also looked at Page rank values of each node in order to make a statement about the importance of the term. Page rank is an algorithm that was originally developed to measure the relative importance of web pages. It formed the basis for ranking results when using the Google search engine and was named after Larry Page (Brin and Page, 1988; Page et al., 1999). Today, Page rank is a common tool in network analysis aiming at assessing linked documents based on their

[6] Available at http://gephi.github.io/

TABLE 1 | Issues and associated topics, characterized by terms that were contained in the final set.

Issue	Topics associated with issue (in brackets: terms that characterize the topic)
Anatomical localization	15 topics: {accumbens, nucleusaccumbens}, {alic, limb}, {amygdala}, {caudatenucleus}, {centromedian, centromedianparafascicularcomplex}, {cingulatecortex}, {cingulum}, {globuspallidus, globuspallidusexternus, globuspallidusinternus, pallidus}, {hippocampus}, {pallidum}, {pedunculopontine, pedunculopontinenucleus}, {stn, subthalamicus}, {subgenual, subgenualcingulate, subgenualcingulatecortex}, {vim}, {zonaincerta}
DBS indication	20 topics: {addiction, alcoholism, smoke}, {alzheimer}, {anorexianervosa, eatingdisorders, obesity}, {anxiety}, {ataxia}, {bradykinesia}, {chorea, huntington}, {clusterheadache, headache}, {depression}, {dyskinesia}, {dystonia}, {epilepsy}, {essentialtremor, tremor}, {hypomania, mania}, {memory}, {obsessivecompulsive, ocd}, {parkinson}, {schizophrenia}, {sclerosis}, {tourette}
Positive effects	3 topics: {qualityoflife, wellbeing}, {alleviation, relief, remission}, {enhancement}
Negative effects	18 topics: {safety}, {aberrant, adverse, adverseevents, complication, decline, deterioration, distress, impairment, perseverative, sequela, sideeffect}, {apathy}, {ataxia}, {character, personality}, {death, die, suicide}, {dysarthria}, {dyskinesia}, {fluency, language, speech}, {hemorrhage, hemorrhage}, {hypersexuality}, {hypomania, mania}, {impulsecontrol, impulsivity}, {infection, inflammation}, {memory}, {pain}, {psychosis}, {psychosocial}
Methodological issues	15 topics: {ablation}, {radiosurgery, ultrasound, gammaknife}, {capsulotomy}, {cingulotomy}, {pallidotomy}, {subthalamotomy}, {thalamotomy}, {psychosurgery, lobotomy, leucotomy}, {computertomography, diffusiontensorimaging, eegfmri, electrocorticography, electroencephalography, fmri, magnetoencephalography, mri, tomography, transcranialsonography, ventriculography, pet, spect}, {spinalcordstimulation}, {transcranialdirectcurrentstimulation}, {transcranialmagneticstimulation}, {vagusnervestimulation}, {electroconvulsivetherapy}, {dopamine, dopaminereplacementtherapy, duodopa, ldopa}
Economic issues	3 topics: {commercial, cost, costeffectiveness, economic, expensive, financial, inexpensive, market, socioeconomic, expenditure}, {industry, manufacture, manufacturer, medtronic, kinetra}, {effectiveness}
Technological issues	3 topics: {battery, cable, device, electrode, hardware, implantablepulsegenerator, lead, pacemaker, recharge, rechargeable, stimulator, wireless}, {closedloop, responsiveneurostimulatorsystem}, {program}

Remind that Lemmatizing in step 3 has mapped most of the different manifestations of topics (e.g., abbreviations) on a single term (e.g., the abbreviation "PD" on "parkinson"). The topics ataxia, dyskinesia, (hypo)mania, and memory are present in two issue classes.

connectivity structure. The principle of this measure can be explained as follows: the more links (in our case connections) refer to a site (in our case to a node/topic), the more weight a given site receives. As a consequence, the more weight a given site/node acquires, the bigger its importance. If one interprets co-occurrence of topics as a measure of "linking" two topics, then the page rank value would determine the order of "search results" in the network determined by the topics chosen by us. Since we are only rarely referring to page rank, we refrain from describing the mathematical basis of this algorithm in detail and refer to the original work by Brin and Page, to a brief description by Chen et al. (2007 p. 9) and to an in-depth review by Langville and Meyer (Brin and Page, 1988; Langville and Meyer, 2004; Chen et al., 2007).

Graphs were represented by use of a Force Atlas 2 algorithm (Jacomy et al., 2014). This algorithm is used to spatialize the network: nodes repulse each other similar to charged particles whereas edges attract their nodes like springs. The specific spatial distribution of each node therefore depends on the nodes' connections to other nodes. As a result, the specific coordinate of one single node cannot be interpreted on its own but has to be analyzed in combination with other nodes (Jacomy et al., 2014). Since edges are weighted, we added the "Edge Weight Influence" δ ($\delta = 3.0$, a pre-programmed selection option) to the visualization in order to prevent edge weights to be ignored.

RESULTS

Trend Analysis over Time

The trend analysis of potential anatomical DBS targets over time suggests a crosscurrent tendency: while the discussion of psychiatric DBS indications such as addiction, major depressive disorder (MDD), schizophrenia, Tourette syndrome (TS), and obsessive-compulsive disorder (OCD) (among others) are increasingly being discussed, the discussion of conventional, motor-related indications such as Parkinson's disease (PD) and essential tremor (ET) recedes (see **Figure 3A**). Dystonia, on the other hand, shows a surprisingly stable pattern over time. In confirmation of the above, the trends for anatomical DBS targets mainly match the ones depicted in the DBS indication analysis: while traditional anatomical targets used in movement disorder therapy decline over time—globus pallidus (GP), ventral intermediate nucleus (Vim), subthalamic nucleus (STN) –, a marked increase of "psychiatric" targets—e.g., nucleus accumbens (Nacc) or subgenual cingulate (SG)—is visible (see **Figure 3B**). Interestingly, the increase of psychiatric targets is less pronounced than the one for psychiatric indications, suggesting that psychiatric indications have become *per se* an emerging topic within the DBS literature. The above described pattern is again partly backed when including the trend analysis for lesion methods (including radiosurgery, capsulotomy, gammaknife, pallidotomy, to name a few) specifically: the discussion of such alternative techniques in the context of motor disorders decreases substantially. Interestingly, there is no trend in the case of psychiatric indications (see **Figure 3C**).

In line with these results is the fact that overall, the trend analysis for negative effects shows an increased emphasis in discussing "psychiatric" phenomena (including anhedonia, hypomania, personality, and impulsivity among others) whereas phenomena associated with traditional, motor related indications (apraxia, ataxia, dysarthria, among others) are consistently less often discussed. Surgery related issues (such as hemorrhage, infection, and ischemia, to name a few) are quite stable. The data also confirm earlier findings (Müller and Christen, 2011) that general terms which indicate side-effects non-specifically such as "aberrant," "adverse," "complication," "distress," "impairment," "sequel," "sideffect" (among others), are also less often mentioned.

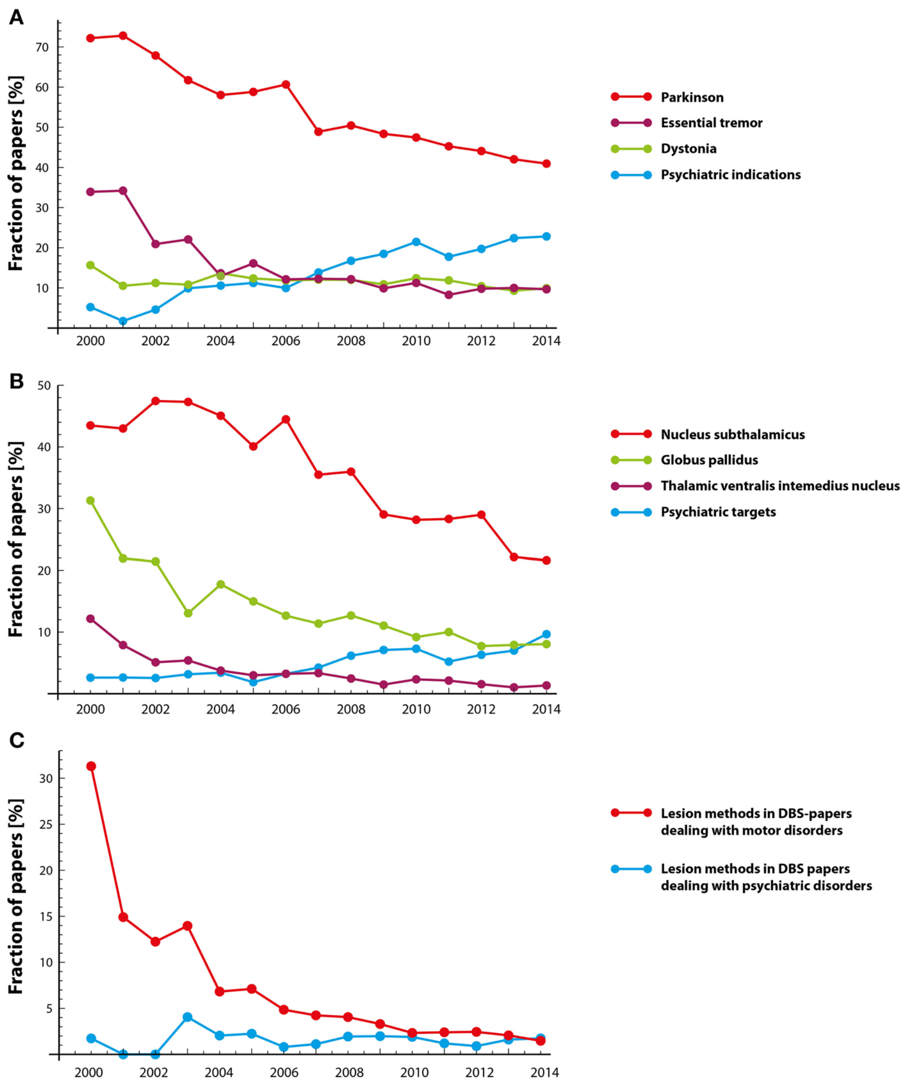

FIGURE 3 | Trend analysis for selected topics. (A) Movement disorders vs. psychiatric indications; **(B)** DBS targets for movement disorders vs. targets for psychiatric indications; **(C)** mentioning of lesion methods in papers also mentioning movement disorders vs. psychiatric indications.

Finally, technological terms associated with new stimulator systems such as "closed loop," "responsive neurostimulator system," "rechargeable," and "wireless" have partly displaced the discussion about conventional technological and hardware-related terms which themselves are less often discussed (e.g., "battery," "cable," "electrode," "implantable pulse generator," "lead," "pacemaker," and "stimulator"; data not shown).

Analysis of Whole Data Set

General Structure of the Graph

Overall, the aggregated graph (except the issue ethic which was analyzed separately) consists of 73 nodes and 1908 edges (**Figure 4**). We observe the average shortest path length to be pretty small (1.3) (Jackson, 2008) (i.e., we can move from one point in the network to another point quite easily, the graph is therefore well-interconnected). The graph furthermore shows a high number of influential nodes besides a high value of average degree (i.e., a quite diverse text corpus). In general, degree is a measurement of connectedness in graph theory which means that a specific node in a given network with high degree consequently has many neighbors in that network. A high average degree therefore means that the graph is highly interconnected. Because of this high average degree, no contextual clusters have been identified using the community detection algorithm of Blondel et al. (2008).

Thematic Structure of DBS Publications

The betweenness centrality (BC) analysis reveals that apparently five main topics dominated the DBS field in terms that they occupied an exceedingly central space within the whole text corpus. Those are effectiveness, safety, side-effects, and hardware related issues apart from PD, the main indication for DBS

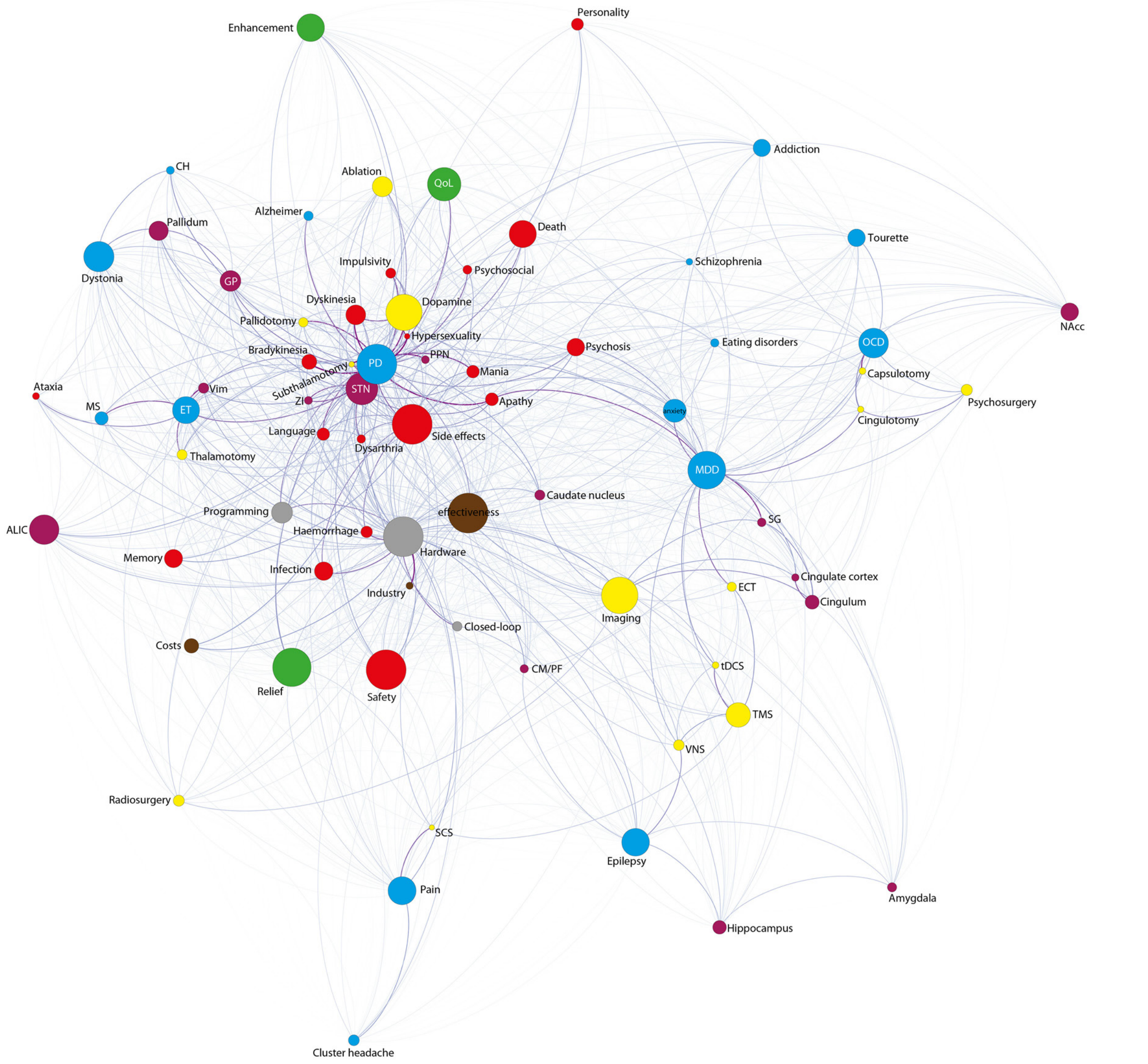

FIGURE 4 | Network of all 73 topics (except ethic). Color-code: Blue: indications; purple: anatomical targets; yellow: methods; green: positive effects; red: negative effects; brown: economic issues; gray: technological issues.

(equal BC values; see **Figure 4** and Table 1 in Supplementary Materials). Moreover, those topics are adjacent to most of the words in the network and therefore function both as local hubs (i.e., a node with many connections) and as important junctions within the whole text corpus.

Apart from the five main topics, the topics including positive effects (alleviation, relief, remission), MDD, imaging methods, dopamine, quality of life (QoL), STN, dystonia, OCD, anterior limb of the internal capsule (ALIC), pain, enhance(ment), epilepsy, death, ET, and imaging methods (with decreasing values across sequence) also show high betweenness centrality. Concrete side-effects appear at place 25 and 27 (dyskinesia and infection). The topics personality (place 41), psychosocial (place 56)—both inherently difficult variables –, subthalamotomy, alternative therapies [such as electro-convulsive therapy (ECT), vagus nerve stimulation (VNS), spinal cord stimulation (SCS), or transcranial direct current stimulation (tDCS)] and hypersexuality [which itself occurs quite rarely (in 19 abstracts only)] (place 72) receive especially low BC.

A Google's page rank analysis revealed the following sequence of importance: PD, hardware related terms, side-effect, STN, MDD, effectiveness, dopamine, ET, imaging-methods, GP, OCD, safety, dystonia, and positive effects (alleviation, relief, remission). The BC values of neuroanatomical targets indicates a higher BC value for ALIC than for GP and a higher one for Nacc than for Vim. However, this sequence changes when conducting Page-rank analysis: highest values are accredited to the STN, GP, ALIC, Vim, and Nacc. Also, the lesional approaches (pallidotomy, subthalamotomy, and thalamotomy) receive dramatically more weight (in the middle field) when performing Page-rank (among lowest if conducting BC).

Analysis of Specific Topics

Next we performed a co-occurrence analysis incorporating the five terms (effectiveness, safety, side-effect, PD, and hardware) with highest BC (see Table 2 in Supplementary Materials for detailed information on all co-occurrence-values). Firstly, the topic effectiveness is most often mentioned in combination with the topics PD and hardware. Likewise, the second topic safety is most often discussed in the context of PD and hardware. Third, we were interested in the topic side-effect, which shows to be, apart from PD, the topic with most above-threshold co-occurrences (co-occurrences > 0.3, determined by the authors based on distribution of the data; see Table 2 in Supplementary Materials). It is most often mentioned with hardware- and motor-related side-effects but also includes side effects of the psychiatric/psychological domain: infection, hemorrhage, dysarthria, apathy, speech, psychosis, memory, mania, dyskinesia, psychosocial, anxiety, hypersexuality, subthalamotomy, STN (among others, with decreasing values across sequence). Fourth, the main indication PD, is discussed to a greater extent with hypersexuality (or more accurately; whenever there is a text including the term "hypersexuality," "parkinson" is most often also present), bradykinesia, subthalamotomy, and apathy. Please note that the term "hypersexuality" appears quite rarely (in 19 abstracts only). The results therefore have to be complemented and analyzed in combination with how often a term actually occurs within the texts (for frequency distributions see Supplementary Figure 1B). The last and fifth key-topic with highest BC includes hardware-related issues which is discussed most often with industry, hemorrhage, new systems (terms: "closed loop," "responsive neurostimulation system"), program, infection, PD, and general economic-topics (terms "cost," "commercial," "economic," "financial" among others).

Analysis of Interactions between Different Issues

In order to investigate on potential interactions of different issues, we conducted a co-occurrence analysis. First we outline the co-occurrence of topics related to the issues indications, anatomical targets, and side-effects.

Interaction between Indications and Side-effects

As for the combination of indications and side-effects (**Figure 5**), the strongest co-occurrence connections yielded the following results. The topic PD is most commonly discussed with hypersexuality (as already stated above). Moreover, PD is often discussed with apathy, dyskinesia, mania, impulsivity, speech (and dysarthria), psychosocial, death/suicide, and psychosis. ET, on the other hand, is most often discussed with dysarthria. Of note is the fact that neither MDD nor dystonia is strongly connected to any concrete side-effect. Additionally, and as a side note, an intracategorial analysis shows most often co-occurring side effects to be impulsivity and hypersexuality.

Interaction between Indications and Anatomical Targets

The combination of indications and targets (**Figure 6**) showed strongest co-occurrence connections between PD and the STN, followed by the pedunculo-pontine nucleus (PPN), the zona incerta (ZI) and lastly with the GP. ET, on the other hand, is clearly connected with the Vim. MDD is most often linked to the SG, the cingulate cortex, and Nacc, while the indications bradykinesia and dyskinesia show most frequent connections to the STN. Finally, OCD is most often discussed with the Nacc and schizophrenia with the hippocampus.

Interaction between Side-effects and Anatomical Targets

Finally, the strongest co-occurrence connections between the issues side-effects and anatomical targets (**Figure 7**) yielded the following results: The STN is most often discussed with apathy, mania, speech, dysarthria, impulsivity, death, and hypersexuality. We found no robust co-occurrence between neuroanatomical targets relevant for the treatment of psychiatric disorders and concrete side-effects (such as infection and the like). Also no marked co-occurrence of side-effects and anatomical targets other than the STN were observed.

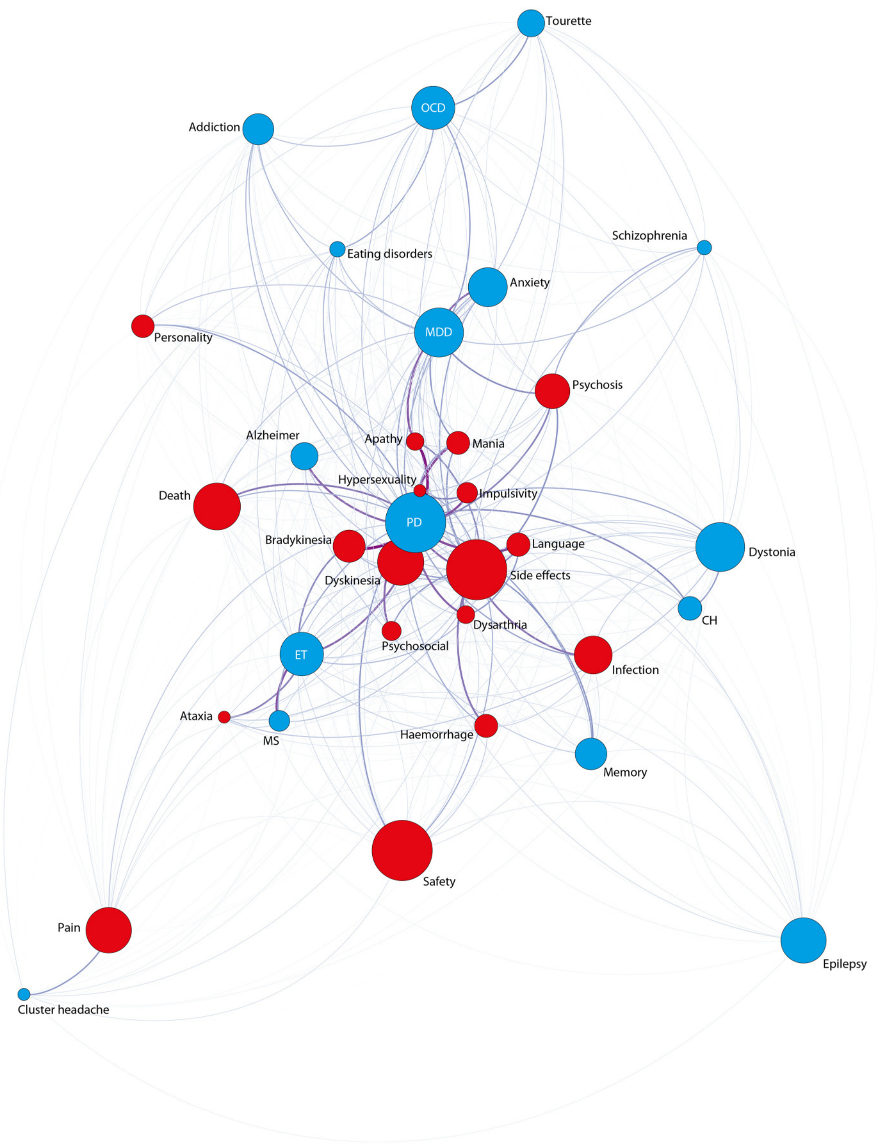

FIGURE 5 | Network-Analysis for the issues indications (blue nodes) and side-effects (red nodes).

Additive Relationships

Additively, we were interested in potential connections between topics from economic issues, technological issues, and positive effects.

The topic industry is most often discussed with PD, imaging methods, safety, and ET. Interestingly, terms like "costs," "economic," "commercial" and the like are markedly linked to the indication PD solely. The issue positive effects including the topics alleviation, relief, and remission are most often associated with PD, pain, and dopamine. The terms "quality of life" and "wellbeing" on the other hand are most often connected to PD, side-effect-related terms, psychosocial, and apathy while most prominent connections with regard to the topic enhance(ment) are PD, hardware, and STN. In particular, the strong connection between QoL and psychosocial is important because it may highlight an increased interest in psychosocial issues in the context of QoL. Finally the topic program is most often discussed with PD and STN whereas the topic of new-devices (terms: "closed loop" and "responsive neurostimulation system") is most often connected to PD and epilepsy.

When integrating how methods other than DBS are discussed within the DBS-literature, one finds the following outcomes:

Concerning indications, PD is most often connected to subthalamotomy, dopamine, and pallidotomy. OCD on the other hand is robustly connected to capsulotomy and to a minor degree to cingulotomy whereas ET is mentioned most often in combination with thalamotomy. Finally, MDD is most often discussed with ECT, cingulotomy and still quite often with tDCS whereas epilepsy is most often discussed with VNS.

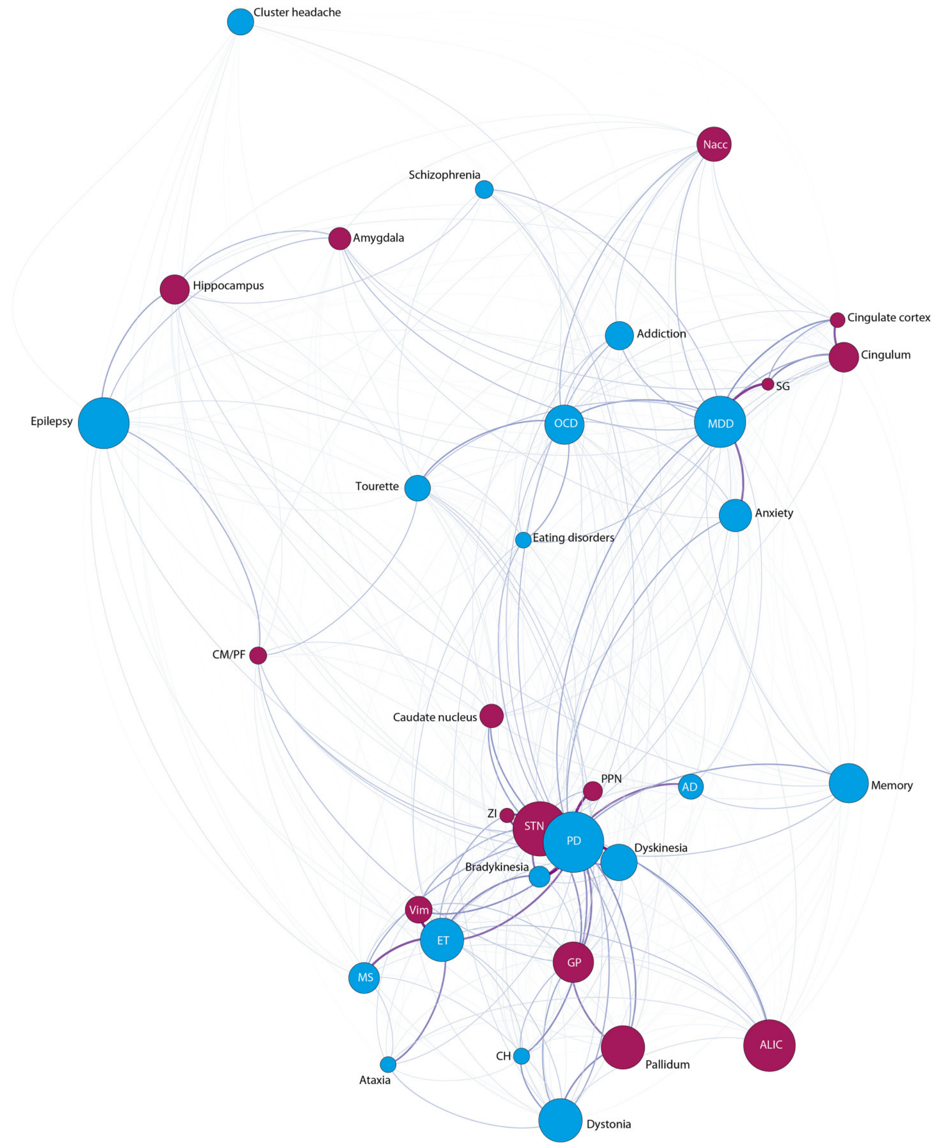

FIGURE 6 | Network-Analysis for the issues indications (blue nodes) and anatomical targets (purple nodes).

Regarding side-effects, dopamine is apparently most often discussed in combination with hypersexuality, impulsivity, psychosis, apathy, and dysarthria. Psychosurgery on the other hand, is mostly discussed in the context of cingulotomy whereas pain (here probably meant as indication) most often with SCS.

Associations with the Topic "Ethic"

There is a rich discussion which deals with ethical aspects in the context of DBS. Ranging from personality changes and side-effects (Christen et al., 2012) to topics taking up the debate of human enhancement (Synofzik and Schlaepfer, 2008; Schermer, 2013) and research ethics (Fins et al., 2011), the discussion is clearly multifaceted. Hence, ethical questions are a constant topic of debate. Therefore, we were interested in how ethics-terms interrelate with other terms of the text corpus. We therefore investigated the co-occurrence of the topic ethics with all other topics (see **Figure 8**). Apart from the rare topic psychosurgery (present in only 52 texts) and the very frequent topic PD (present in 3544 texts) which yielded the strongest co-occurrences, the ethics-topic is most often linked to personality, psychosocial, side effect, hardware, MDD, and hypersexuality. Of note is the very rare connection between ethical issues to the GP (in only 3% of the total possible co-occurrences) compared to the STN (in 14% of the total possible co-occurrences).

DISCUSSION AND CONCLUSION

We will first outline some of the findings which underpin the validity of our approach directly followed by discussing

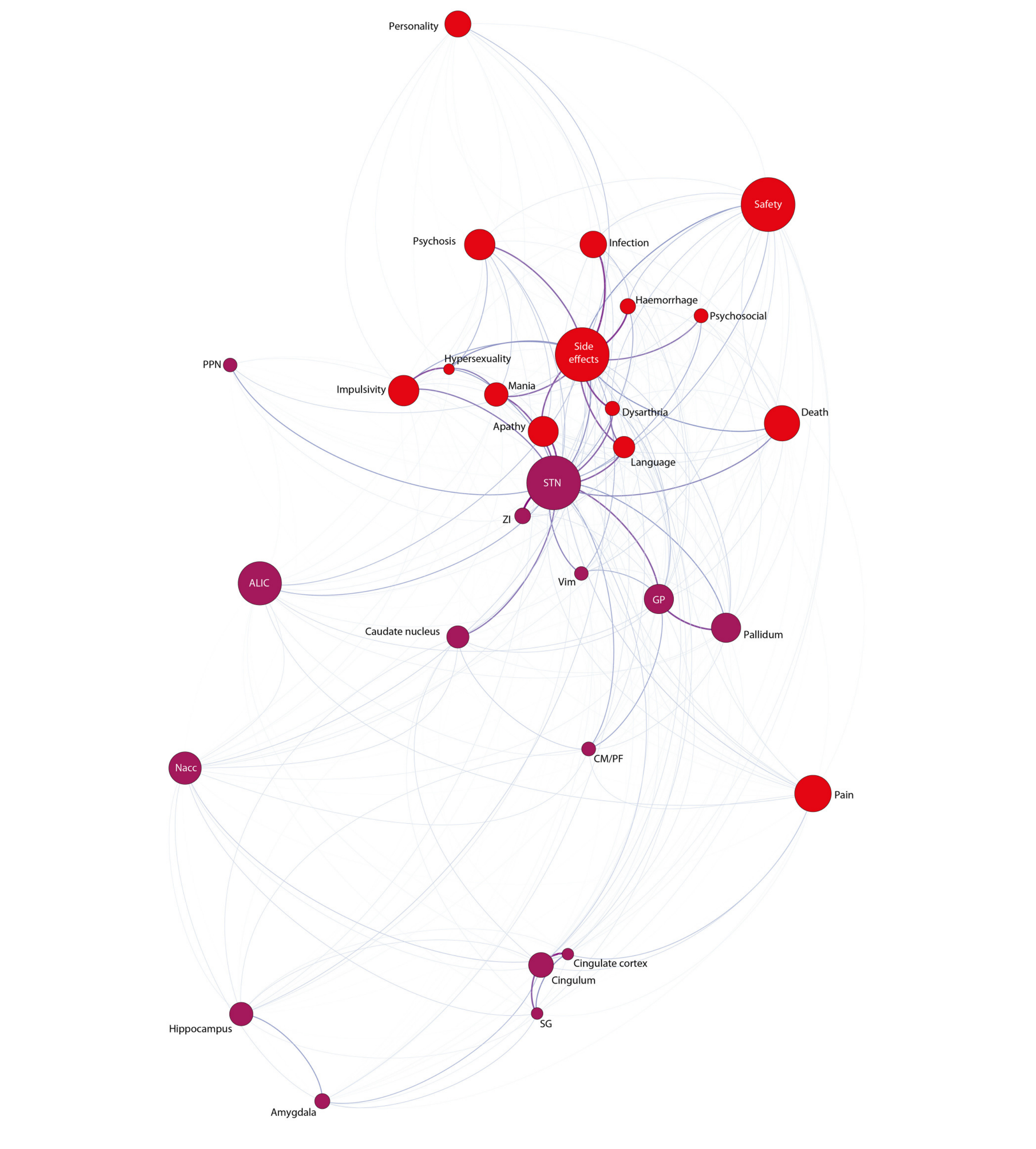

FIGURE 7 | Network-Analysis for the issues negative effects (red nodes) and anatomical targets (purple nodes).

findings acquired from the trend analysis over time and then guide the discussion toward the graph analysis based on BC and co-occurrence. Finally, we will outline pertinent ethical questions.

Findings Corroborating the Validity of Our Approach

We detected a multitude of findings which underpin the validity of our approach, some of which we highlight in the following.

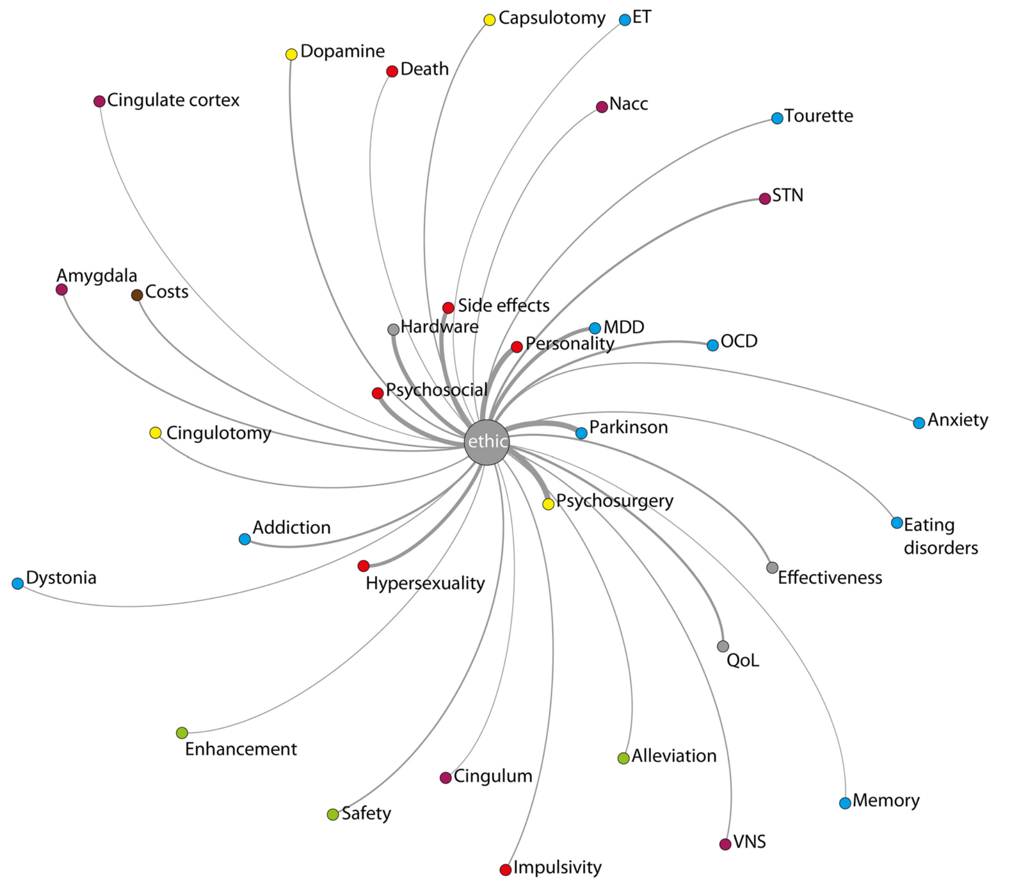

FIGURE 8 | Interrelation of the topic ethics to all other topics with at least 5% co-occurrence (for color code see caption of Figure 4).

Chronic pain for example, is a well-described indication suitable for spinal cord stimulation (Wolter, 2014). The findings including indications and lesion methods also confirm known connections as evidenced in the case of ECT, a well-known therapeutic option for the treatment of MDD, besides others. The relationship of epilepsy and closed-loop systems might also underpin the robustness of our methodological approach by bearing in mind that epilepsy characterizes a promising indication for the application of closed loop devices (Armstrong et al., 2013; Krook-Magnuson et al., 2013; Paz et al., 2013; Nagaraj et al., 2015). Regarding anatomical targets and side-effects, we highlight a distinct connectivity between the STN and impulsivity which has been described elsewhere (Zavala et al., 2015). Regarding the detected intracategorial connection between impulsivity and hypersexuality, a recent publication confirms a tight connection between the two topics (Kor et al., 2013). Hence, a multitude of identified co-occurrences incorporating the different issues such as indications and corresponding lesion methods, or indications and anatomical targets among others, serve as validation of our method.

Trend Analysis

When analyzing the data set including DBS-indications and relevant anatomical targets, one can identify a clear shift away from motor-related neuroanatomical targets (GP, Vim, STN) (even though numerically still predominant) toward an emphasis on anatomical targets which are especially relevant in psychiatric indications (Nacc, amygdala, hippocampus, SC) (see **Figures 3A,B**). Such a tendency is indicative for the broadening of the therapeutic spectrum of DBS. A multitude of scientific publications highlighted this circumstance already (e.g., Hariz, 2012; Hariz et al., 2013; Christen et al., 2014, to name a few). Even though we cannot make a qualitative statement about how such topics are being discussed (i.e., the discussion may be framed in a supportive, critical, or neutral way), the identified increase may represent the seen utility in DBS for the treatment of psychiatric indications. Questions about suitability of such complex disorders for the therapeutic application of DBS and the difficult search of anatomical loci for the treatment of such indications (e.g., for MDD (among others): Nacc, ALIC, and SG) may also be indicative for such an increase. Additionally, the data highlights no standard locus for the treatment of MDD (e.g., Hariz et al., 2013 for the unspecific use of neurostimulation targets in the context of MDD, TS, and OCD; or Da Cunha et al., 2015; Kocabicak et al., 2015). Finally, the trend analysis incorporating negative effects (data not shown) completes the picture; while motor side effects are less frequently discussed, complex issues such as personality are increasingly the topic of the current debate. In the context of psychiatric disorders, such phenomena seem to be prevalent to a greater extent.

The trend analysis involving lesion based therapy approaches revealed that lesion approaches recede in the context of motor-related disorders and are quite stable in the case of psychiatric disorders. This might demonstrate—and under the assumption that medication based therapy is still the most frequently used therapeutic approach—that (1) lesions are still considered to be an effective and reliable means for patients refractory to drug-therapy and (2) that DBS was not (yet) able to replace lesion-based therapy approaches in psychiatry. When talking about an observed decline of the discussion of topics related to lesion approaches, one has to emphatically point out that this reflects how lesions are being discussed within the DBS-literature only. This means that we are limited in our interpretation of observations related to lesion methods and look with a narrow "DBS-perspective" on relationships which are discussed in these articles. Moreover, lesion approaches are still considered therapeutic competitors and as such might receive little attention. We have outlined elsewhere (Christen et al., 2014, but see also Müller et al., 2015) the importance of ensuring alternative therapeutic approaches which of course would not quantitatively carry much weight when extracting abstracts from numerous DBS-publications.

Network Analysis

Thematic Structure of DBS Publications

Our results suggest that the topics PD, side-effect, hardware, safety, and effectiveness play a conducive role within the DBS literature and this to a greater degree than other terms because the relation of their influence to the total number of connections was calculated to be highest (reflected in BC). One could say that the backbone of any publication in the context of DBS is composed of issues about safety, side-effects, effectiveness, hardware, and PD. These junctions act as mediators within the discursive field of the textual graph. The broader backbone of a publication in the field of DBS can be inferred to be generated through the mentioning of the remaining major topics: relief, MDD, imaging methods, dopamine, QoL, STN, dystonia, OCD, ALIC, pain, enhance(ment), epilepsy, death, ET, and TMS. This furthermore means that by analyzing the top 20 terms and by allocating those to the major topics, it is evident that indications are most numerously represented ($n = 7$), followed by negative effects ($n = 4$), methods ($n = 3$), and anatomical targets ($n = 2$). As the discussion in the DBS literature is shifting toward new and more specific questions, specific anatomical targets tend to be less often associated with more general topics. The strong representation of indications again reflects the trend of broadening the therapeutic spectrum in the context of DBS.

Personality and Psychosocial Issues in DBS Publications

The growing discussion about personality (trend analysis) is not yet reflected in BC because the topic personality shows one of the lowest BC-values. This can be explained by referring to the low frequency of the topic itself within the whole text corpus and may likely change as such issues have to be addressed in the context of measuring pre-post-effects in the case of psychiatric neurostimulation. The circumstance of personality and psychosocial issues receiving low BC may indicate that their associated concepts represent genuinely vague and difficult variables and consequently are not utterly useful for clinical research. As validated instruments to objectively and qualitatively measure changes in the personality and the psychosocial dimension are often missing or criticized for not accurately measuring the topic under investigation, such much needed concepts cannot easily enter clinical research (Dimitrov and Rumrill, 2003). The fact that psychiatric indications are increasingly being addressed by means of brain-stimulation, the need for the accurate and thorough observation and measure of psychosocial and personality-related issues (and also in the context of movement and other disorders, Pham et al., 2015) is obviously most important. Therefore, with more accurate insights into the neuronal circuitries exerting maladaptive effects on many disorders despite high complexity and limited means of investigation (Rossi et al., 2015) and the eagerness to evaluate results beyond short-term quality of life (Ooms et al., 2014), indications for DBS should get more individually tailored (Galati and Stefani, 2015). Additively, the accurate and longitudinal measure of psychosocial issues has already been proposed also in the context of movement disorders (Schüpbach and Agid, 2008). Combined with the fact that the topic QoL is robustly connected to the topic psychosocial, as well as the fact that a limited number of scales for the measurement of personality- and psychosocial-related issues do exist, the introduction of such instruments combined with the eagerness to improve such instruments, is greatly needed.

Economic Issues

The restriction of the discussion incorporating economic issues to PD only, also poses questions. Given the increase of psychiatric indications, economic considerations should be in place and extended toward other indications in order to adequately address socio-economic issues. The often observed co-occurrence between the topic economic and ethic further emphasizes this point.

Centralities of Neuroanatomical Targets and Their Implications

The BC-values of neuroanatomical targets indicate a higher one for ALIC than for GP and a higher one for Nacc than for Vim. This may serve as another evidence for the growing importance of neuropsychiatric topics in the literature of DBS. However, this sequence changes when conducting Page-rank analysis: highest values are accredited to the STN, GP, ALIC, Vim, and Nacc. Since Page-rank puts an emphasis on the number of connections (e.g., "links"), the traditional motor targets STN and GP would be listed before ALIC within a given search result. Given the fact that GP and Vim represent historically older topics in DBS and based on the higher Page-rank values, the two are more densely linked with other topics. However, ALIC and Nacc already are more central concepts within the DBS-literature, presumably acting as mediators of information to a greater extent than GP and Vim.

MDD and Alternative Therapeutic Approaches

The execution of a Page-rank analysis also changes the sequence of the most important topics: PD clearly is attributed the highest value and MDD makes it into the "top 5." In sum, one can state that depression is the most discussed psychiatric indication in the DBS literature. In light of MDD's importance within the DBS literature, it is from a bioethical point-of-view important to emphasize that this indication has not yet received approval from the U.S. Food and Drug Administration (FDA) as a standard therapeutic treatment. Patients therefore should be well-informed about the ongoing search of optimal neuroanatomical targets, the challenging support without standardized guidelines of patients along the whole treatment and beyond as well as the complexities associated with the appropriate conduct of clinical trials (Jimenez-Shahed, 2015) and the vulnerability of patients (Bell et al., 2014).

When looking specifically at alternative therapeutic approaches such as SCS, tDCS, ECT, and VNS, it becomes obvious that they receive especially low BC. This circumstance can be explained by highlighting that we specifically selected scientific publications involving DBS. Presumably, those publications have a low interest in advocating for alternative therapeutic approaches. Furthermore, the co-occurrence analysis shows that within the DBS-literature, ablative therapeutic approaches such as pallidotomy, subthalamotomy, and thalamotomy are most frequently discussed in combination with terms from the topic side effect. While ablative therapeutic strategies appear to a greater degree to be negatively connoted, the latter also symbolize the still most direct competitors to DBS, as already outlined within the trend-analysis. Interestingly, the lesional approaches (pallidotomy, subthalamotomy, and thalamotomy) receive dramatically more weight (in the middle field) when performing Page-rank (among lowest BC). In analogy of the previous hypothesis, lesion approaches might be underestimated if incorporating BC only and seem to be interlinked to a greater extent.

Discussion of Issue-comparisons

The specific comparison involving indications and side-effects indicates that the description of side effects is clearly dominated by the ones closely associated with PD, the indication for which most publications exist ($n = 3544$, followed by essential tremor, $n = 901$). This does not mean that PD is the DBS indication where most side effects occur, but that side effects are most frequently described in the context of PD. As outlined above, the strong connection between PD and hypersexuality only reflects that within the few papers dealing with hypersexuality, the term "parkinson" is almost always present. Since the topic hypersexuality is very infrequent, this result has to be taken with caution. On the other hand, one also has to take into account that our data consist of abstracts only, i.e., terms need to have some importance within a paper in order to appear in the abstract. Side effects of other indications, especially neuropsychiatric, are to a far lesser degree discussed. Depression for example co-occurs only to a minimal extent with personality, death, and psychosocial issues. As highlighted previously, side effects in the context of psychiatric disorders are expected to be (1) much harder to be identified and (2) still have to be published as such newer indications have only recently been added to the therapeutic spectrum. OCD with its unconventional entry into the therapeutic landscape via a humanitarian device exemption (Fins et al., 2011) is also quite rarely discussed in the context of concrete side effects [probability of co-occurrence: hypersexuality (11%), impulsivity (8%), and infection (5%)]. Again, there is a duty to longitudinally follow patients in order to constantly monitor potential side-effects, besides the great need for introducing new measures in order to fully capture potential changes also in the psychosocial/psychiatric domain (Lilleeng et al., 2015).

The comparison involving indications and neuroanatomical targets highlights a further interesting result: apart from being discussed most often with the STN, PD is also quite strongly connected to the PPN, even more than to the GP—the other standard target for stimulation apart from the STN. PPN-stimulation was initially promoted for the treatment of balance impairments as well as refractory gait freezing and has been shown to be used as surgical target relatively unspecifically ("the PPN-area") and this despite largely unknown clinical usefulness (Hariz et al., 2013). The high centrality of the PPN together with such a critical stance toward its usefulness and lack of clinical evidence further corroborates an apparent tension.

Finally, when comparing side-effects and anatomical targets, we observe again a dominant description of side-effects in combination with the STN—one of the most widely used anatomical targets for the treatment of movement disorders. The most frequent co-occurrence of the GP is its connection to apathy, but this happens only in 7.5% of cases in which a possible co-occurrence is possible. This, potentially driven by stimulation of ventral and medial subterritories of the STN (for STN-subterritories see Tremblay et al., 2015; for actions beyond motor control see Zavala et al., 2015), reflects a described dominance of side-effects in the context of STN rather than other (e.g., GPi) DBS targets. Moreover, this could indicate that side-effects emanating from predominantly ventral STN-stimulation have overshadowed the description of side-effects of other anatomical targets such as the GP. Alternatively, the STN may be intrinsically more prone to (behavioral or affective) side effects due to its circumscribed connectivity to limbic areas. There is evidence for a clearer separation of motor and non-motor functions in the GPi compared to the STN (Wichmann and DeLong, 2011; Da Cunha et al., 2015). Additionally, ALIC, an anatomical target with marked BC, is rarely found in combination with specific side effects. This imbalance may be problematic or may be the result of the already mentioned problem of capturing side-effects in the context of psychiatric disorders. However, if DBS for the neuropsychiatric domain further expands, the accurate description combined with the nuanced measurement of psychological changes poses a bioethical obligation and responsibility for any researcher involved. It might be an interesting endeavor to once try to capture the implicit perception of professionals in the field of DBS regarding such issues. The numerical imbalance of how e.g., anatomical targets are discussed in relation to side-effects together with the concrete framing of such issues within the most often read articles in the literature supposedly induce unconscious preferences which do not necessarily display the situation in an accurate way based on (pre-)clinical evidence.

Bioethical Issues

As the field of bioethics is comparably subjected to a vast increase of publications, quantitative methods for obtaining a better understanding might be as important as for neuroscience. Such an approach is moreover suitable for identifying potential mismatches between what is currently being discussed and what might be important ethical topics which are less tangible or more vulnerable for being overlooked.

Motor-targets and Their Connection to Ethics

Apparently, ethical issues are to a greater extent discussed in combination with the STN rather than the GP. Is the STN therefore more thoroughly described in terms of its stimulation-based ethical consequences or is there evidence that the STN intrinsically harbors to a greater extent problematic ethical issues including the potential of inducing undesired effects? The debate of which target is most appropriate (mostly including STN and GP, Follett et al., 2010; Krack and Hariz, 2010; Odekerken et al., 2013) is an old one. But since currently, there is evidence for a statistical chance selection rather than one based on (patho)-physiological evidence for either receiving STN or GP stimulation (Christen et al., 2014; Gilbert, 2014) [besides clinical considerations such as envisaging drug reduction (STN) or preexistence of cognitive symptoms (GPi) (Da Cunha et al., 2015)], this difference might be an important one. As long as there is no proven display regarding superiority in terms of therapeutic action, there might be a duty to investigate ethical issues to a similar extent for all nuclei used for stimulation.

Depression and Its Connection to Ethics

Another interesting finding is an observed imbalance reflected in a strong connection between the issue which incorporates the topic ethics on the one hand and MDD on the other and a substantially weak connection of the former topic and the one involving the most often used anatomical targets in the context of depression. Whenever ethical issues are being discussed, MDD is most often also discussed. However, the factual co-occurrence dramatically decreases in the case of neuropsychiatric anatomical targets: ethical issues co-occur only in 6.5% of cases when discussing the Nacc, in 3.5% when discussing the ALIC and in 1.75% when discussing the SG. This apparent dissociation between indication and anatomical target is questionable and more pronounced as in the case of PD and STN. As DBS has not faced a comparably long history regarding randomized controlled clinical trials for psychiatric disorders, studies have to be continued in order to identify which nucleus (or nuclei) shows greatest potential for the treatment of MDD and other neuropsychiatric disorders but also to identify which nucleus might be especially vulnerable for (behavioral) side-effects, psychosocial maladjustments and consequently ethical issues (e.g., non-maleficence).

Hardware Related Issues

As evidenced in some publications (Kondziolka et al., 2001; Okun et al., 2005; Fins, 2009) hardware related complications do impose ethical challenges. This is also backed by our results highlighting an apparent tension between hardware and ethical issues. Concomitantly, our data set indicates a continuous decrease of the discussion of hardware related topics (evidenced in the trend analysis; data not shown) but also particularly high BC. The strong link to ethical issues, apart from the mere description of hardware-related side-effects, might be evaluated as unintuitive. However, the data suggests that hardware related issues in the context of social, ethical and moral questions apparently have already been a topic of debate (e.g., Hilimire et al., 2015; Fumagalli et al., 2015). Generally, the topic of ethical and social implications of technological devices is certainly an important one which, e.g., in the context of emerging closed-loop devices, will nourish further discussions in the future. Therefore, closely investigating ethical, social, and clinical aspects of the follow up process longitudinally, including e.g., the often challenging postoperative phase for precise DBS parameter adjustments (Ineichen et al., 2014) as well as fiscal and legal aspects of hardware replacement apart from ethical issues specifically in the context of hardware is important. In parallel, our result may emphasize not only a duty to investigate hardware related ethical issues which transcend merely and well-known technical problems (Christen et al., 2014) thoroughly, but also that ethical duties already instantiated also apply to engineers which represent key players and which are well-positioned to support the deployment of innovative hardware in order to diminish the burden of patients (Fins, 2009). In the general DBS review literature, hardware-related issues such as the ones attached to recording devices and the related implications for patients' autonomy and responsibility but also the potential use and abuse of such recorded signals in connection with privacy issues, the dependency on device manufacturers (Underwood, 2015) and conflicting interests (Clausen, 2011), the long-term risk of living with implanted hardware (Farris et al., 2008) apart from psychological issues have in comparison to surgical complications probably received less attention. The fact that hardware-related issues receive dramatically more weight in the context of ethical challenges than impulsivity, concrete side-effects and death/suicide is certainly surprising and needs further analysis. Whether this means that hardware-related issues are already sufficiently discussed in an ethical and social context or need further exploration has to be identified by a qualitative in-depth analysis.

Although DBS has alleviated patients suffering tremendously, many obstacles still remain. Recently, the development of innovative neuromodulation exemplified by current steering (Martens et al., 2011; Hariz, 2014b), adaptive DBS (Little et al., 2014) but also the potential deployment of closed-loop devices (e.g., Rosin et al., 2011; Grahn et al., 2014; Williams, 2015) have increasingly gained weight within the discussion of DBS. In the meanwhile, magnetothermal neuromodulation in translational models (Chen et al., 2015) shows potential to increase our knowledge of neuronal microcircuitries (Temel and Jahanshahi, 2015). Apart from technological as well as biological hurdles (e.g., identification of true biomarkers) also ethical issues might arise. As our data highlights a tremendously weak co-occurrence of the topics ethics and closed-loop, it might be time to think about how emerging closed-loop devices may affect already instantiated guidelines and what differences as well as implications might be identified both from a theoretical (i.e., philosophical) but also practical (i.e., what it would mean for patients) perspective.

Limitations

This study, of course, incorporates some limitations. First of all, as in any quantitative text-network approach, we are unable to make qualitative statements. This however, is within the nature of a heuristics approach. Additionally, various topics might in fact be used in a different context than used as a basis for interpretation within this study. For example, the neuroanatomical targets may in fact very well also be mentioned without referring to a target for stimulation. For example, the STN may be described within a DBS-publication not as a target for stimulation but within the context of hyper-reactivity in the case of hemiballism. Due to the fact that we have limited our analysis to abstracts, we assume this scenario to be quite infrequent and would hypothesize such a wording to be included in a general introduction rather than within an abstract. Moreover, the Web of Science database is associated with a language bias. As papers emphasizing psychosocial and philosophical issues are often published in other languages, they are likely to be underrepresented in our sample. Finally, topics which incorporated multiple terms, of course, inevitably have a greater probability of co-occurrence.

Outlook

The proposed analysis is by no means complete and has no prerogative of accuracy. It is one additional possibility to read any text in order to gain new insights about its structure and hidden messages, suitable to deal with a large number of texts. We are of the opinion that applying network approaches, visualization techniques and graph theory to a text corpus might be an innovative and promising alternative which entails fruitful and worth considering aspects. The final interpretation of the data, once visualized as a graph, is certainly open for discussions and by no means definitive.

Hariz recently wrote in his book chapter "The literature revisited" that "serendipitous discoveries and advances in functional imaging are providing 'new' brain targets for an increasing number of pathologies, and the corollary is an exponentially growing literature on DBS, such that it is simply impossible to keep track of all papers and books appearing on this subject." He then goes on by stating "While most of the literature constitutes an invaluable wealth of knowledge, a small but important part gives rise to serious concern and needs to be revisited and discussed" (Hariz, 2014a). By using a quantitative network approach, we tackled this issue from another perspective and tried to identify potentially hidden and underrepresented issues which might be relevant for further discussions and future research.

AUTHOR CONTRIBUTIONS

CI extracted the data, MC generated the final set, CI and MC analyzed the data and wrote the paper. CI furthermore confirms that he has final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnint.2015.00052

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Publication 2: Understanding the global practice of DBS

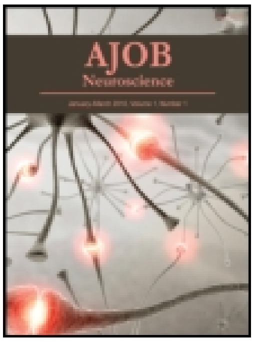
Synopsis

In order to achieve insights into the global practice of DBS, we performed a survey among DBS centers (n = 135) and experts (n = 113). The following results frame the problem of conflicting outcome interpretations (discussed in the introduction) and provide elements which might constitute tension-points in the context of psychosocial and behavioural management post-operatively.

In terms of decision making, we discovered some mismatch between fears patient mention frequently and the actual risks. The results highlight that the frequency of patient fears and expert assessment of risk probability differ. Surgical complications are mentioned often by patients, although their incidence is small; technical problems and personality changes are less often mentioned, although they are more frequent. The fact that patients rather seldom raise issues like technical problems with the device and postoperative personality changes due to stimulation might indicate an information-gap between patients and experts. This may partly be responsible for the relative high prevalence of satisfaction gaps reported.

We also found that complex changes in behaviour ("personality changes") and the "satisfaction gap" seem to be more common problems than expected: 26.5% of the experts believed that "personality changes" may occur in more than 5% of the cases. 38.0% of the experts believed that "satisfaction gaps" occur in more than 10% of the cases (30%,11-20% & 8% >20%). When asking for likely causes for the emergence of personality changes, 43.4% of the experts considered stimulation to be the more likely cause of personality changes compared to changes in medication. The experts described personality changes both as an increase as well as decrease of a patient's activity level.

With respect to the institutional dimension, we find a surprisingly fast dynamic with respect to the expansion of DBS indications: 12% of all centers already perform DBS for depression (research trials) and 40% of all centers plan to offer a therapeutic intervention for depression within the next 5 years. Depression therefore is the indication which is most frequently planned to be offered by the centers.



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Ethical Focal Points in the International Practice of Deep Brain Stimulation

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Target Article

Ethical Focal Points in the International Practice of Deep Brain Stimulation

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Deep brain stimulation (DBS) is a standard therapy for several movement disorders, and the list of further indications that are investigated is growing rapidly. We performed two surveys among DBS experts ($n_1 = 113$) and centers ($n_2 = 135$) to identify ethical focal points in the current global practice of DBS. The data indicate a mismatch between the patients' fears and the frequencies of the suspected side effects, a significant "satisfaction gap," signs of improvements of outcome, habituation effects in terms of involved disciplines, a growing spectrum of novel indications that partly conflicts with the experts' success probability ratings, and differences in the density of supply between countries that might affect the future development of DBS. We formulate ethical recommendations with regard both to patient-related practices (e.g., recruitment, assurance of alternatives) and to institutional development (e.g., measures for quality assurance and for the development of novel DBS indications).

Keywords: deep brain stimulation, movement disorders, psychiatric disorders, patient management, center development, biomedical ethics

Deep brain stimulation (DBS) reflects a fundamental shift in the understanding of neurological and psychiatric diseases: namely, as resulting from a dysfunctional activity pattern in a defined neuronal network that can be normalized by targeted stimulation. DBS has been developed since the 1950s (Hariz et al. 2010); its "modern era" began in the 1980s (Benabid et al. 1987; Siegfried 1986). In recent years, the application of DBS has grown remarkably (Müller and Christen 2011) and is increasingly investigated as a therapy option for various intractable neurological and psychiatric disorders (Goodman and Alterman 2012; Holzheimer and Mayberg 2011), primarily for obsessive-compulsive disorder (OCD) (De Koning et al. 2011) and major depressive disorder (Anderson et al. 2012; Schläpfer et al. 2013). The spectrum of indications for which DBS is used in pilot studies is rapidly expanding; it comprises drug addiction (Luigjes et al. 2012), Tourette's syndrome (Müller-Vahl 2013), aggressive and disruptive behavior (Franzini et al. 2012), severe obesity (Halpern et al. 2011; Whiting et al. 2013), anorexia nervosa (Lipsman et al. 2013a), and Alzheimer's disease (Hardenacke et al. 2013; Laxton and Lozano 2013; Laxton et al. 2010). To date, DBS has been approved (European CE mark) in Parkinson's disease (PD), essential tremor (ET), dystonia, epilepsy, and obsessive-compulsive disorder (OCD).

The beneficial effects of DBS on motor functions are well established (Deuschl et al. 2006; Kleiner-Fisman et al. 2006; Wider et al. 2008). The evaluation of cognitive, affective, and behavioral sequelae of the intervention (Videnovic and Metman 2008; Volkmann, Daniels, and Witt 2010; Witt, Daniels, and Volkmann 2008) is nontrivial, as they may result from surgery, stimulation, or drug reduction, and—in particular in PD—similar effects can result both from disease progression and from medication. Taking these issues into account, the focus of research is shifting to practical issues like decision-making of patients, psychosocial effects of the interventions, and optimal long-term care. Thus, DBS has become an established therapeutic option with new indications on the horizon.

We propose to investigate the practice of DBS along two dimensions: The first dimension relates to all processes that influence the individual intervention (patient-related

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dimension), and the second relates to the development of the infrastructure (infrastructure-related dimension). The first dimension involves information of patients, the referral practice, exclusion criteria, decision-making, the intervention, and the follow-up (Clausen 2010; Kubu and Ford 2012; Lipsman et al. 2012). The infrastructure-related dimension captures aspects of the development of the DBS infrastructure that are decisive for high-quality interventions. This includes issues like the emergence of new DBS indications, involvement of different disciplines, differences in the DBS procedures between centers (e.g., target preferences), center capacities, the financing of DBS research, and the long-term planning of center development given the growing spectrum of DBS indications (Abosch et al. 2013; Bell, Mathieu, and Racine 2009; Fins et al. 2012).

In order to obtain an overview of the global practice of DBS we performed two surveys: a survey of researchers/clinicians and a survey of DBS centers. The surveys addressed the decision-making process of patients, disciplines involved in the DBS procedure, target preferences of centers, exclusion criteria, risk evaluation, outcome analysis, expert opinions about characterization, incidence and causes of "personality changes" following DBS, and a possible "satisfaction gap" (Agid et al. 2006; Kluger et al. 2011). Furthermore, the surveys collected data that allows for assessing the referral practice, trends for novel indications, and the experts' opinions with respect to controversial DBS issues. Cross-comparison of both surveys allowed for validating the results.

MATERIALS AND METHODS

Survey of Experts

The anonymous survey of DBS researchers and clinicians was performed in two waves between mid 2011 and mid 2012, each of them including two follow-ups (by e-mail). The first wave addressed researchers identified by us (Christen et al. 2012) who published about DBS in Parkinson's disease since the early 1990s. The second wave addressed clinicians whom we identified in a global search of DBS centers. Both search strategies were complemented by bibliometric research to ensure that those 100 authors who published most on DBS are included in the data set. For all persons identified we searched for valid e-mail addresses. In total, 656 persons with valid e-mail addresses have been approached. Since 22 of them did not publish about DBS for more than 10 years, it is unlikely that they are still active in the field, so that the universal set consists of 634 researchers and clinicians.

The survey questionnaire was developed based on previous research (Christen et al. 2012; Christen and Müller 2011; Müller and Christen 2011) and has been cross-checked by a board of researchers (see acknowledgments). It included 31 questions; the mean responding time was 20.5 minutes.

Survey of Centers

The non-anonymized survey of centers that offer DBS interventions was restricted to 12 countries that ranked highest in the number of DBS research papers published: Australia, Canada, England, France, Germany, Italy, Japan, the Netherlands, Spain, Sweden, Switzerland, and the United States. For these countries we have performed an Internet-based search to find clinics (public and private) that offered DBS according to their website at least sporadically in 2010 or 2011. This was complemented by bibliometric research to identify home institutions of persons that published on DBS. Five hundred and thirteen institutions that claim to offer DBS have been identified. The questionnaire was sent to these institutions by postal mail in June 2012; two follow-ups were performed (via e-mail, until October 2012). In the postal mail, we included the list of all centers of the respective country and asked the responsible person to check the list for completeness and for false entries. We also approached all 12 national neurosurgical associations and the leading DBS supplier Medtronic to check our lists. Based on the feedback, we identified 408 sites in the 12 countries that were confirmed to offer DBS or that are likely to do so at least sporadically. The questionnaire for the survey of centers included only eight questions, to promote a high response rate. It had been pretested in a Delphi study among all Swiss DBS centers (Christen and Müller 2012).

Both the surveys of experts and the survey of centers did not need approval from the responsible ethical review committee (Kantonale Ethikkommission Zürich) given our institutional guidelines, as patients were not addressed by the surveys and no information was collected that could be related to individual patients. Furthermore, we followed the CHERRIES guidelines (The Checklist for Reporting Results of Internet E-Surveys; see http://www.jmir.org/2004/3/e34) as far as they were applicable.

Bibliometric Study and Literature Search

Using the Thomson Reuters Web of Science database, we performed a bibliometric study on January 26, 2012, to check the completeness of our expert database. On December 6, 2012, we identified the funding sources mentioned in DBS papers. The study was accompanied by a study of the DBS literature for identifying controversial issues, and we consulted our review board to make a selection. In addition, we searched for papers for estimating the incidence and prevalence of the major DBS indications. Since we found that the data is rather controversial, we restricted the research to PD, where the data is most reliable. We used Mathematica 9.1 for statistical calculations.

RESULTS

Survey of Experts

One hundred and twenty-three persons provided answers in the survey of experts. Ten persons were excluded due to the low number of answers provided (less than 50%), leaving usable data of 113 persons (response rate: 17.8%; see also Table 1). Ninety-nine experts answered all questions. We note that the search of experts included all (co)authors of DBS papers published since 1991; therefore, most of them were not principal investigators and probably many do not work in the field of DBS anymore. Hence, many of the approached persons may have been reluctant to provide answers, since they are not "true" DBS experts. Thus, the reported response rate is the lower limit of the "true" response rate of experts who are still active in the field of DBS. The DBS core disciplines neurosurgery (46.9%) and neurology (39.8%) are most represented in the expert sample. The median age of the responders was 48 years, and their majority is male (72%). The five most represented countries of origin (17 in total) were the United States (23.9%), Germany (13.3%), France (12.4%), Italy (12.4%), and the United Kingdom (4.4%).

Survey of Centers

One hundred and thirty-five institutions provided answers to the survey of centers. The overall response rate was 32.8% (see also Table 1); the response rates of the countries varied between 54.5% (Canada) and 23.6% (the United States); the response rate of 100% in Switzerland results from the fact that the pretest of the survey included all Swiss centers. The total number of patients that received a DBS intervention in the responding centers is at least 29,350, that is about one-third of an estimate of 85,000 patients that have received a DBS intervention globally (data as of January 2011; Christen and Müller 2012).

Validating Expert Experience

On average, the centers in which the experts work (in the following, "expert centers") had started DBS treatments earlier and had implanted more patients than reported in the survey of centers (data not shown). This indicates that the expert centers tend to be experienced above average. Of the responding experts, 69.9% had treated at least 100 patients; 68.1% are regularly or often involved in research (clinical, basic, validation, technology); 77.0% have expert knowledge in patient selection, 77.9% in patient follow-up, 65.5% in surgery, 64.6% in patient information, 58.4% in device programming; and 36.3% in novel DBS applications. Based on these findings, we conclude that the sample of the survey of experts consists mainly of experienced DBS researchers and clinicians.

Patient-Related Dimension of DBS Practice

The first dimension of DBS practice concerns the intervention process in individual patients: that is, the information of patients, the referral practice, exclusion criteria, decision making, the intervention, and the follow-up. The complete results are contained in Figure 1, Table 2, and Table 3.

Information of patients and referral practice. With respect to information sources used by the patients and to the referral of patients to DBS centers, the neurologists (in private practice) seem to be the decisive "entry point" to DBS (Table 2).

Exclusion criteria. Dementia is the most important reason for excluding a patient from a DBS intervention, followed by general medical risk factors, the psychiatric history, and the age of the patient (Table 3).

Decision making. According to the experts, most patients uttered the hope for symptom relief, followed by more independence, enjoying life again, and going back to work. The patients' greatest concerns are surgery-caused problems, followed by technical problems, death, personality changes, and being remote-controlled. The frequency of fears uttered by the patients does not always match with the experts' assessment of risk probability. Particularly, surgical complications are mentioned often by the patients, although they have the lowest probability according to the DBS experts, whereas fears of technical problems and of personality changes are less often mentioned by the patients, although the experts consider these sequelae to be more frequent (Figure 1a).

Intervention. In the course of the DBS intervention for movement disorders, a broad spectrum of tests is used: Motor functions, medication dose, cognitive functioning, and mood are always checked before and after the intervention. Emotional functioning, language, quality of life, and social functioning are not always, but still routinely part of the assessment procedure. Other aspects like sleep, autonomous functions, weight change, and sensory systems are often, but not routinely, part of the assessment. The before–after comparison is insufficiently monitored

Table 1. Response rates of the center and expert surveys

	Experts	Centers
Initial set of experts/centers that have been approached	656	513
Confirmed or likely set of experts/centers active in DBS	634	408
Valid responses	113 (18%)	135 (33%)
Experts/centers that operated at least 100 patients	79 (70%)	77 (57%)

Figure 1. Patient-related dimension: (a) Frequency that the patients express specific hopes and fears in the DBS decision-making process. (b) Assessment of personality change by the experts. (c) Assessment of the satisfaction gap by the experts.

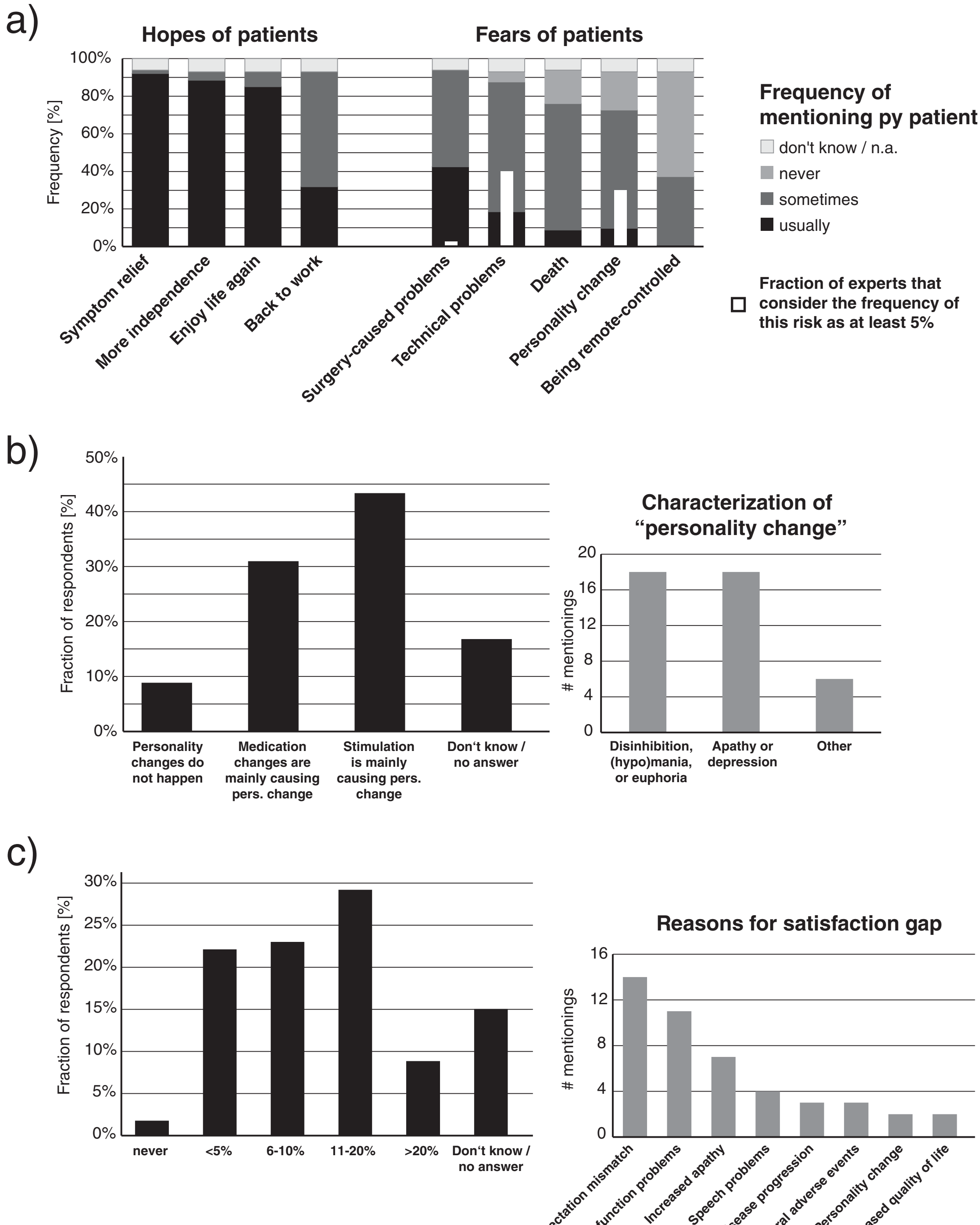


Table 2. Factors characterizing the DBS intervention process: information sources of the patient, referral of the patient, and the frequency of exclusion criteria used in patient selection based on the survey of experts

	Usually/often	Sometimes	Never	Don't know/no answer
Information sources of the patient				
Neurologist in private practice	76.1%	19.5%	0.9%	3.5%
Physician of the DBS institution	53.1%	30.1%	8.8%	8.0%
Internet	53.1%	42.5%	0.0%	4.4%
Support groups	47.8%	40.7%	5.3%	6.2%
Brochure of the DBS institution	42.5%	31.0%	17.7%	8.8%
General media	31.0%	50.4%	8.0%	10.6%
Family and friends	24.8%	67.3%	1.8%	6.2%
Brochure of the device producer	23.9%	46.9%	21.2%	8.0%
General practitioner	11.5%	53.1%	22.1%	13.3%
Scientific literature	12.4%	58.4%	17.7%	11.5%
Referral of the patient by...				
... neurologist in private practice	91.2%	8.0%	0.0%	0.9%
... other medical institutions	47.8%	41.6%	6.2%	4.4%
... departments of the same institution	37.2%	38.9%	12.4%	11.5%
... himself/herself (self-referral)	20.4%	48.7%	20.4%	10.6%
... the general practitioner	15.9%	59.3%	19.5%	5.3%
Frequency of exclusion criteria				
Dementia	71.7%	21.2%	0.9%	6.2%
General medical risk factors	40.7%	50.4%	1.8%	7.1%
Psychiatric history of the patient	38.9%	53.1%	0.9%	7.1%
Age of the patient	37.2%	50.4%	6.2%	6.2%
Insufficient compliance suspected	21.2%	57.5%	12.4%	8.8%
Unrealistic expectations by the patient	22.1%	53.1%	15.9%	8.8%
Alcohol addiction	19.5%	38.9%	32.7%	8.8%
Drug addiction	23.0%	28.3%	39.8%	8.8%
Anxiety of the patient	8.0%	46.9%	37.2%	8.0%

only for weight changes, as eight participants in the survey of experts reported that weight is an issue only before the intervention, but not after.

Follow-up. In the bioethical literature on (subthalamic nucleus [STN]) DBS, two issues of follow-up received particular attention, namely, the possibility of "personality changes" and the "satisfaction gap," i.e., physicians express satisfaction with the result whereas patients are less satisfied. Personality changes as understood in psychology refer to alterations in the "Big Five" personality traits (i.e., extraversion, neuroticism, agreeableness, conscientiousness, openness to experience; see Costa and McCrae 1992), and it is known from the literature that (STN) DBS can influence each of these in some patients (Müller and Christen 2011). We have exemplified the term with examples like hypomania, hypersexuality, aggressivity, and risk-taking behavior. We found that 26.5% of the experts believed that "personality changes" occur in more than 5% of the cases, 38.1% estimate their incidence at 2–5% of all cases, and 23.9% believe that they happen in less than 1% of the cases (11.5%: don't know). Of the experts, 43.4% considered stimulation to be the likely cause of personality changes compared to changes in medication (Figure 1b). The experts described personality changes after DBS mostly as alterations of mood: The patients became either more depressive and apathetic or more hypomanic.

The issue of a satisfaction gap is not uncommon: 38.0% of the experts believed that it occurs in more than 10% of the cases, 23.0% estimate its prevalence at 6–10%, and 23.9% think that it happens in 5% of the cases or less (15.0%: don't know). The experts mention a multitude of reasons, particularly an expectation mismatch, but also motor function problems and increased apathy (Figure 1c).

The experts reported lower incidences of adverse effects for the case of apathy, depression, and language problems than reported in the literature about STN DBS in PD (Table 3). Of the experts, 67.3% document adverse effects (publications, database, or standardized reporting form), although only 12.4% indicated a reporting obligation.

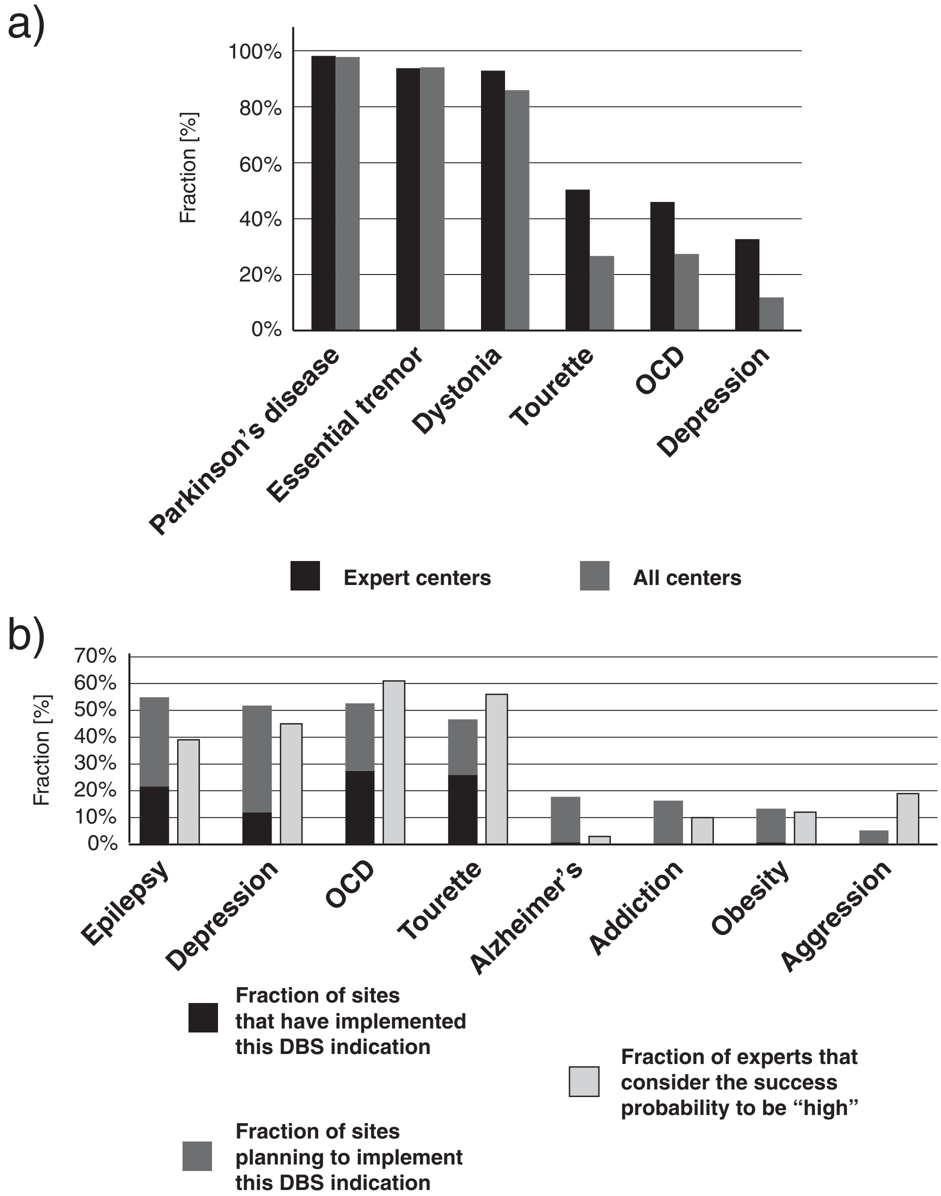
The time span for device programming varied over a remarkably broad spectrum: 10 experts claim to use less than 4 weeks for device programming, 29 use 4–8 weeks,

Table 3. Comparing the ratings of the experts of the frequency of side effects of STN-DBS in PD patients with data of outcome reviews

	<1%	1–5%	6–10%	11–20%	>20%	Don't know/no answer	Literature
Apathy	27.4%	26.5%	15.9%	15.0%	2.7%	11.5%	12–25% [a] 3.5% [b] Up to 24.6% [c]
Language problems (dysarthria)	20.4%	33.6%	22.1%	8.0%	5.3%	10.6%	9.3% [d] 12.8% [b]
Device problems (e: lead fracture; d: electrode or wire replacement; b: malfunctioning, premature loss of battery power, acute failure of the stimulator, etc.)	23.0%	30.1%	29.2%	5.3%	1.8%	10.6%	0–15% [e] 4.4% [d] 4.4% [b]
Personality change (d: manic episodes; f: personality changes, hypersexuality, apathy, anxiety, aggressiveness; g: manic psychosis; a: hypomania; b: hypomania, hypersexuality)	23.9%	38.1%	15.0%	7.1%	4.4%	11.5%	1.9% [d] <0.5% [f] 0.9–1.7% [g] 4–15% [a] 1.2% [b]
Depression	16.8%	44.2%	20.4%	4.4%	1.8%	12.4%	6.8% [d] 8% [f] 1.5–25% [a] 20–25% [g] 4.3% [b] 20–25% [c]
Anxiety	35.4%	30.1%	10.6%	7.1%	1.8%	15.0%	2% [f]
Hemorrhage (f: symptomatic intracranial hemorrhage)	67.3%	19.5%	0.0%	1.8%	0.9%	10.6%	0–10% [e] 3.9% [d] 2.0% [b]

Note. Sources of data: [a] Voon et al. 2006; [b] Videnovic and Metman 2008; [c] Witt et al. 2012; [d] Kleiner-Fisman et al. 2006; [e] Bronstein et al. 2011; [f] Temel et al. 2006; [g] Volkmann et al. 2010.

Figure 2. Infrastructure-related dimension: (a) Overview of current main DBS indications offered by centers. (b) Comparison of the frequency of (planned) application of DBS for novel indications with the success evaluation of the experts.



28 use 9–12 weeks, 16 use 13–24 weeks, and 2 experts use more than 24 weeks (not involved in programming or "don't know": 28).

Infrastructure-Related Dimension of DBS Practice

The second dimension concerns the institutional development of DBS, particularly the offer of new DBS indications, multidisciplinary teams, differences of the DBS procedures (e.g., different target preferences), center capacities, the financing of DBS research, and the long-term planning of center development given the growing spectrum of DBS indications. The detailed results are contained in Figure 2 and Tables 4, 5, and 6.

New DBS indication. Almost all centers offer DBS for PD, ET, and dystonia, but also Tourette's syndrome, OCD, and depression are quite common indications (Figure 2a). DBS for Tourette's syndrome is performed by 25.9% of the centers (and by 50.4% of the expert centers); for OCD by 27.4% (46.0% of the expert centers); and for depression by

Table 4. Annual numbers of patients that have received a DBS intervention

	Annual number of patients that received a DBS intervention				
	<10	10–20	21–50	51–100	>100
Survey of experts (excluding 5 that currently do not work in a DBS site)—data of 2010	15.9%	29.0%	33.6%	13.1%	8.4%
Survey of centers: mean numbers for 2009 to 2011 (excluding 4 that did not provide data)	21.4%	37.4%	32.8%	8.4%	0.0%
Survey of centers: current capacity (excluding 1 that did not provide data)	7.5%	27.6%	40.3%	20.9%	3.7%

Note. First row: annual numbers reported in the survey of experts (expert centers); second row: annual numbers reported in the survey of centers. The experts reported higher numbers than the centers, reflecting the fact that the experts tend to work at sites that perform more interventions. However, 9 experts reported working at a site that operates on more than 100 patients—a number that is not met by the reporting of the centers. Potential reasons for this mismatch are that some expert centers may not be present in the data of the survey of centers (the survey of experts was anonymous), slight differences in the questions (the experts reported the number of surgeries in 2010, the centers a mean estimate of the last 2–3 years, i.e., 2009 to 2011), or over-/underreporting of the experts or centers.

11.9% (32.7% of the expert centers). For epilepsy, depression, OCD, and Tourette's syndrome, about half of the centers either offer DBS currently or plan to implement it in their programs within the next 5 years (Figure 2b). Further indications that are planned to be offered in the next 5 years by some centers are Alzheimer's disease (17.0% of the centers; one center already does research in this field), addiction (16.3%), obesity (12.6%), and aggression (5.2%). When these numbers are compared to the fraction of experts who expect a high success probability for these indications, two discrepancies have to attract attention: First, 17% of the centers plan to treat Alzheimer's disease with DBS, although only 3.0% of the experts consider the success probability to be high, whereas 68.0% consider it to be low. Second, only 5.2% of the centers plan to treat aggression with DBS, although 19.0% of the experts consider its success probability to be high.

Multidisciplinary teams. In routine DBS interventions, 60.7% of the centers involve at least two additional disciplines besides the core disciplines neurology and neurosurgery, for example, (neuro)psychology, care, rehabilitation, or social work. Centers that offer DBS not only for movement disorders but also for further neurological and psychiatric disorders involve significantly more disciplines (3.61 disciplines in the mean) than those centers that restrict DBS to movement disorders (2.89 disciplines) (Mann–Whitney; $p < .002$).

Differences of the DBS procedures (e.g., different target preferences). Because of the discussion about the optimal target of DBS in Parkinson's disease, particularly about the STN (stimulation of which can address more symptoms than the other targets, but it has higher risks of psychiatric side effects; Hariz et al. 2008), we investigated the preferences for different stimulation targets for Parkinson's disease. We found a considerable difference with regard to the preferred stimulation target between U.S. and European centers: By weighting the survey entries of target frequencies (usually = 4, often = 3, sometimes = 2, rarely = 1) we found a relative distribution of STN, globus pallidus pars interna (GPi), and nucleus ventralis intermedius (VIM) target preferences of 74.4%/19.9%/5.6% for European and 60.4%/31.9%/7.7% for U.S. centers. When additionally weighting this data by the number of patients the centers operated, the distribution is 72.7%/20.7%/6.6% for Europe and 54.5%/33.6%/11.9% for the United States. These results show that European PD patients are more likely to be stimulated in the STN than were U.S. patients.

Center capacity. Of all DBS centers (survey of centers), 58.8% operated on 20 or fewer patients per year (Table 4). Given the current infrastructure, 64.9% of the centers would have the capacity to operate on more than 20 patients per year. We estimated whether the number of centers available and their capacity match with the expected number of patients that qualify for DBS in PD. The prevalence of PD in industrialized countries is around 0.3% of the entire population; reported standardized incidence rates are 8–18 per 100,000 person-years (De Lau and Breteler 2006). Table 5 gives a rough prediction of the eligibility rate of PD patients, that is, the number of PD patients per year that could qualify for DBS given an estimate of the available capacity and the annual incidence of PD (the number of patients that all centers could operate per year divided by the number of new PD patients per year). The data reveal a large variance of the estimated eligibility rate between the different countries.

Funding. The bibliometric study revealed indications of a difference in public funding for DBS between the United

Table 5. Estimating the capacity of DBS centers of 12 countries based on the most important indication (PD)

	AUS	CAN	CHE	DEU	ENG	ESP	FRA	ITA	JPN	NLD	SWE	USA
Number of responding centers	5	6	7	14	5	11	11	16	9	4	2	45
Total capacity of responding centers	237	196	193	562	143	316	336	255	265	140	73	2’655
Total number of centers	10	11	7	44	18	28	25	30	30	8	6	191
Estimated capacity of country per year	470	360	200	1770	510	800	760	480	880	280	220	11’270
Total population of country (in Mio; 2012)	22.5	34.3	8.0	81.9	53.0	47.2	65.4	60.6	126.7	16.7	9.5	314.2
Estimated number of PD patients (in 1,000)	67.5	102.9	24.0	245.7	159	141.6	196.2	181.8	380.1	50.1	28.5	942.6
Number of centers per 1,000 PD patients	6.8	9.4	3.4*	5.7	8.8	5.1	7.8	6.1	12.7	6.3	4.8	4.9
Estimated number of new PD patients per year (in 1,000)	1.8–4.1	2.7–6.2	0.6–1.4	6.6–14.7	4.2–9.5	3.8–8.5	5.2–-1.8	4.8–10.9	10.1–22.8	1.3–3.0	0.8–1.7	25.1–56.6
Predicted estimated eligibility rate	11.5–26.1%	5.8–13.1%	13.9–31.3%	12.0–27.0%	5.3–12.1%	9.4–21.0%	6.5–14.5%	4.4–9.9%	3.9–8.7%	9.3–21.0%	12.9–28.9%	19.9–44.8%

Note. The country abbreviations are according to the ISO 3166-1 alpha-3 standard. The numbers of the total population per country are based on www.wikipedia.de (November 2012).
*The number of DBS centers in Switzerland will be reduced to 4 (or 3) (Christen and Müller 2012), i.e., the number of centers per 1,000 PD patients will be 6.0, or respectively 8.0.

Table 6. Overview of experts' opinions towards claims about DBS

	Strongly disagree	Disagree	Indifferent	Agree	Strongly agree
Lesion surgery versus deep brain stimulation (DBS) in movement disorders					
Lesions are part of the past, they should not be performed anymore	14.2%	37.7%	18.9%	19.8%	9.4%
It's acceptable to offer lesions to patients who do not have a health assurance that will pay for the following costs of DBS and who cannot pay them on their own.	25.7%	20.0%	19.0%	26.7%	8.6%
Lesioning may be acceptable in some cases only if noninvasive methods (e.g. gamma knife) are used.	12.3%	30.2%	33.0%	22.6%	1.9%
It's acceptable to offer lesions to patients who probably will not comply with postoperative care.	4.8%	21.0%	22.9%	44.8%	6.7%
I expect that soon there won't be experts who master lesion procedures.	1.0%	24.8%	27.6%	39.0%	7.6%
It's acceptable to offer lesions in poorer countries if DBS is too expensive.	4.7%	17.0%	17.0%	46.2%	15.1%
For some patients, lesions may be a valid alternative to DBS.	7.5%	5.7%	9.4%	64.2%	13.2%
Unilateral versus bilateral DBS procedures for movement disorders					
Unilateral procedures should be the standard.	16.5%	51.5%	27.2%	3.9%	1.0%
The question of uni-/bilaterality is of secondary importance.	10.5%	41.9%	21.0%	21.9%	4.8%
Bilateral procedures should be the standard.	2.9%	16.3%	20.2%	35.6%	25.0%
The question of uni-/bilaterality depends on the symptoms or other prerequisites of the patient.	1.0%	7.6%	8.6%	43.8%	39.0%
General opinions with respect to DBS in movement disorders					
DBS surgery has a high risk of complications.	20.8%	51.9%	9.4%	15.1%	2.8%
DBS in movement disorders is still a last-resort treatment.	19.8%	47.2%	17.0%	14.2%	1.9%
DBS is a completely reversible procedure.	2.8%	37.7%	17.0%	38.7%	3.8%
DBS in PD is more cost-effective than medication.	2.8%	17.0%	33.0%	40.6%	6.6%
Patients with movement disorders should be able to obtain DBS even when the disease is still manageable by medication.	0.0%	18.9%	20.8%	49.1%	11.3%
DBS should be offered only in large centers.	1.0%	6.7%	16.2%	57.1%	19.0%
More patients should have the opportunity to obtain DBS.	0.0%	1.9%	15.1%	55.7%	27.4%
DBS in movement disorders allows for a better management of disease symptoms than medication alone.	0.0%	1.9%	6.6%	39.6%	51.9%
General opinions with respect to DBS (all indications)					
I have a bad feeling when I learn about the increasing number of possible DBS applications.	26.5%	45.1%	18.6%	8.8%	1.0%
There is an economic interest to offer DBS as a novel therapeutic approach for other diseases than movement disorders.	4.0%	7.9%	22.8%	55.4%	9.9%
DBS will allow us to understand the neurological basis of psychiatric diseases.	0.0%	3.9%	28.4%	45.1%	22.5%
DBS will be an option for the treatment of severe, otherwise untreatable psychiatric diseases.	0.0%	0.0%	23.5%	56.9%	19.6%
DBS has the potential to substantially improve our therapeutic spectrum for various diseases.	0.0%	0.0%	5.0%	62.4%	32.7%

Note. Between 6 and 10% of the respondents did not answer particular questions; they have been excluded in percentage calculations for the respective questions.

States and Europe: Of all U.S. papers, 19.8% mention public funding by governmental institutions, whereas only 5.3% of the European DBS papers do so. In the DBS papers that mentioned a funding source, 53.9% of funding came from companies or private foundations. However, only 1,753 out of 8,016 DBS papers identified (21.9%) contained explicit information on funding that was accessible in Web of Science. This means that this data do not by far reflect all funding sources for DBS. It is likely that many papers do not reveal this information, if the funding source is public. Thus, the result may only indicate differences in funding disclosure between the United States and Europe in the sense that authors from the United States are more likely also to mention public funding.

Finally, we collected the opinions of the experts on various controversial issues raised in the DBS literature. Table 6 provides a summary of the results. In the following, we outline the most important findings.

Lesion surgery versus DBS in movement disorders. The majority of the responding DBS experts (51.9%) do not consider lesion procedures as part of the past that should not be performed anymore. A great majority (77.4%) thinks that lesion procedures are a valid alternative to DBS for some patients. Particularly, the majority agrees with offering lesion procedures in poorer countries (61.5%) or to patients who probably will not comply with postoperative care (51.5%). Almost half of the experts expect that soon there won't be experts who master lesion procedures (27.6% are indifferent; 25.8% disagree).

DBS for movement disorders. Although a majority thinks that bilateral procedures should be the standard (60.6%), most experts think that the question of uni-/bilaterality depends on the symptoms or other prerequisites of the patient (82.8%). Only a minority (17.9) thinks that DBS surgery has a high risk of complications. Interestingly, the majority considers DBS not to be a last-resort treatment (67.0%) and that it should be offered even when the disease is still manageable by drugs (60.4%). The majority supports the claim that DBS should be offered only in large centers (76.1%).

DBS for novel indications. The great majority of the experts (76.5%) endorse the expansion of indications for DBS in favor of the enrichment of the therapeutic spectrum for various diseases, and only a minority (9.8%) utters a bad feeling when they learn about the increasing number of DBS indications. Nevertheless, the majority (65.3%) also thinks that there is an economic interest to offer DBS as a novel therapeutic approach for diseases other than movement disorders. Great agreement occurs also in the opinion that DBS will allow us to understand the neurological basis of psychiatric diseases (67.6%).

DISCUSSION OF ETHICAL FOCAL POINTS

We have investigated the current practice of DBS along two dimensions: (1) the patient-related and (2) the infrastructure-related dimension. We now carve out the ethical focal points in the current practice of DBS.

Patient-Related Dimension

For the patient-related dimension, we found that neurologists are key players both for information and for referral of patients. This finding highlights the importance of an adequate and up-to-date training of neurologists in private practice about DBS. Correct information is necessary, as a timely elucidation about DBS, as well as responding to the individual concerns by the consulting physician, is essential for the acceptance of the treatment (Südmeyer et al. 2012). Adequate expertise is necessary, as movement disorder specialists are more likely to identify good candidates for DBS (Katz et al. 2011). The development of DBS requires that neurologists are regularly informed about new indications, technological improvements, and newly investigated risks.

Data from the survey of experts show that only a minority of patients utter concerns about technical device problems or stimulation-induced personality changes, whereas the experts consider these risks as relevant. This indicates an information gap between patients and experts. We propose that this information gap may be partly responsible for the relatively high prevalence of the satisfaction gap reported by a considerable number of experts. However, other aspects may contribute to this gap as well: The finding that the experts´ ratings of the frequency of the DBS sequelae apathy, depression, and language problems tend to be lower than reported in the literature may indicate a decreased sensibility for the patient's own experience of side effects, although we consider this as less likely (see further discussion). Another potential reason is that even in case of sufficient information the fact that the patient him- or herself experiences side effects may contribute to the satisfaction gap. These hypotheses require further empirical investigation on patients' expectations and how these expectations or other factors determine the evaluation of outcome by patients (e.g., retrospection of the preimplantation health status).

Another relevant finding concerns the mismatch between the experts' ratings of the frequency of the DBS sequelae apathy, depression, and language problems compared to the literature. However, we do not interpret this in the sense that the experts underestimate risks. Rather, the result more likely reflects an improvement in practice not captured by reviews that usually refer to studies some time ago; this, however, needs additional support. More problematic may be that in DBS for movement disorders the number of involved disciplines tends to decrease and that the majority of experts use less device programming time than a recent review on this matter suggests (3–6 months during 4–5 programming sessions; Bronstein et al. 2011). This indicates a habituation effect for established indications that may be positive with respect to cost-effectiveness, but not adequate to the complexity of DBS in PD.

An interesting finding is that the majority of experts of our survey has a relatively positive attitude regarding lesion procedures in movement disorders. More than two thirds believe that they are a valid alternative to DBS for some patients, but also almost half of the experts expect that soon there won't be experts who master lesion procedures. Also in the literature there is support to keep lesion procedures as an important alternative for appropriately selected patients both for movement disorders (e.g., Parkinson's disease; Bronstein et al. 2011) and psychiatric disorders (Leiphart and Valone 2010) like OCD or anorexia nervosa (Barbier et al. 2011; D'Astous et al. 2013; Greenberg, Rauch, and Haber 2010; Kondziolka, Flickinger, and Hudak 2011). In particular, an international expert panel has recently stated in a consensus paper that "until scientifically proven otherwise, DBS is not superior to ablative surgery for psychiatric disorders" (Nuttin et al. 2014). However, the main disadvantage of lesion surgery is that possible negative effects are not reversible. Adverse effects that have been reported are the development of undesirable personality traits (after subcaudatetractotomy) and transient mania and memory deficits (after cingulotomy) (Feldman, Alterman, and Goodrich 2001). We also remark that there are research initiatives for additional noninvasive lesion procedures like focused ultrasound (Jolesz and McDannold 2014; Lipsman et al. 2013b) such that novel expertise in ablative surgery may emerge.

Infrastructure Dimension

With respect to the infrastructure-related dimension several aspects require advertence. First, 60% of the centers operate 20 or less patients per year, although 20 patients per year are considered to be the minimum quantity for DBS training centers (Krauss et al. 2009) and although the large majority of experts think that only large centers should offer DBS. This finding indicates that measures might be necessary to ensure quality also in centers with low case numbers.

Second, we found a rapid expansion of new indications for DBS. About half of the centers presently perform or plan to perform DBS for epilepsy, depression, OCD, and Tourette's syndrome. However, research on DBS in particular for psychiatric indications is in an early state, and success rates cannot be estimated correctly, particularly because of the presumed publication bias (Schläpfer and Fins 2010). DBS is also planned for indications with considerable prevalence, in particular obesity (the prevalence of obesity varies nearly 10-fold among Organization for Economic Cooperation and Development [OECD] countries, from as low as 4% in Japan and Korea, to 30% or more in the United States and Mexico; OECD 2012) and Alzheimer's disease (according to the World Health Organization [WHO 2012], the number of people globally who are living with dementia in 2011 is estimated to be 35.6 million, and studies indicate that this number is expected to grow at an alarming rate). However, only a small minority of experts considers the success probabilities for these diseases to be high. This indicates that societal need partly triggers the expansion of DBS indications. In the case of Alzheimer's disease, it's worthwhile to mention that dementia is considered to be the most common exclusion criteria for DBS in case of PD. This tension that may have an influence on DBS exclusion criteria is discussed neither in recent reviews (Hardenacke et al. 2013; Hescham et al. 2013; Laxton and Lozano 2013) nor in case studies (Fontaine et al. 2013; Laxton et al. 2010) on DBS in Alzheimer's disease. We identified only one comment that points to potential problems when selecting patients suffering from dementia in clinical DBS trials (Salma, Vasilakis, and Tracy, 2014).

Although more than three-fourths of the experts endorse the expansion of indications for DBS in favor of the enrichment of the therapeutic spectrum for various diseases, two-thirds also think that there is an economic interest to offer DBS as a novel therapeutic approach for diseases other than movement disorders. Evidence on cost-effectiveness of DBS is still limited. A recent study for DBS in the case of PD in the United Kingdom calculated a total of discounted costs in the DBS and best medical treatment groups over 5 years of £68,970 and £48,243, respectively. The quality-adjusted life years (QALYs) were 2.21 and 1.21, giving an incremental cost-effectiveness ratio of £20,678 per QALY gained. Thus the results suggest that DBS may be a cost-effective intervention in patients with advanced PD who are eligible for surgery.

Finally, given these dynamics, the capacity of DBS centers may become an issue in some countries. Unfortunately, there is very little research that estimates the fraction of patients eligible for DBS even for the most important indication, PD. Early estimations range from 1.6% to 4.5% (Morgante, Morgante, and Moro 2007) but have been criticized as underrating the ratio of eligible PD patients (Cacciola 2008). Several factors contribute to this underrating: Referring clinicians may underestimate the number of suitable patients (Oyama et al. 2012), women are underrepresented in those referred (Setiawan et al. 2006), and the amount of suitable candidates could increase if patients were referred earlier to DBS (Charles et al. 2012; Schüpbach et al. 2013). Therefore, a more reasonable guess is that 10–20% of PD patients may qualify for DBS (Christen and Müller 2012). Given our findings, countries like Canada, England, Italy, and Japan may have insufficient capacities for dealing with the expectable patient load, which may also affect research regarding novel indications.

CONCLUSIONS AND ETHICAL RECOMMENDATIONS

In summary, our findings indicate a dynamic development of DBS with respect to various issues. To ensure the ethical future of DBS, more emphasis than hitherto should be put on issues that are not directly related to the intervention, but to issues like the referral practice, the expansion of DBS indications, the financing of DBS research, and the development and quality control of DBS centers. We suggest that the following aspects should become focal points of the ethical discussion about DBS.

Patient Dimension

- Entry points: In movement disorders, the neurologists in private practice are the gatekeepers for patient information and patient selection; that is, they frame significantly whether and how patients will consider DBS as a therapy option. In light of the rapid expansion of DBS indications, we should start to think about who will be the gatekeepers for DBS for patients suffering from addiction, depression, OCD, anorexia nervosa, or severe obesity and what we should expect from them (Christen and Müller 2013).
- Reducing the satisfaction gap: A significant number of patients seem to be dissatisfied with the outcome of their DBS treatments. Various reasons may account for this, and it is likely that psychological and social factors play an important role. This phenomenon needs further empirical research, and results of this research should be incorporated as soon as possible in the shared decision-making process with patients.
- Multidisciplinary teams: Our study found indications of habituation effects, which regularly occur when a therapy becomes more and more accepted. An important point is the number of experts that are routinely involved, which is lower in centers that treat only movement-disorder patients, although it is known that PD as well as its treatment (DBS and medication) may involve psychiatric effects. Centers should ensure that sufficiently qualified personnel of several disciplines (including psychiatry) can be called in case they are needed.
- Documenting the outcome: Clinics should follow each of their patients long enough to evaluate improvements in practice and possible long-term sequelae. This should also include case registries on a national level. Outcome analyses help to prevent the repetition of former failures and to establish a good practice (Lieberman et al. 2008).
- Ensuring alternatives: The growing confidence in DBS as a treatment option should not suppress alternative treatments. We support to further investigate lesion procedures (performed by either microsurgery, thermocoagulation, or particularly by Gamma Knife) as an alternative to DBS for particular groups of patients, and to compare their efficiency, risks, and side effects with DBS. There are two important reasons for providing the option of lesion procedures: first, the relative low cost (which is particularly important in poorer countries); and second, certain exclusion criteria or practical limitations of DBS (e.g., patients who could tolerate neither the stress of an operation awake nor an operation under full anesthesia; patients for whom a craniotomy is contraindicated; patients who would not tolerate implanted devices; or patients who live in remote areas such that compliance with the long-term follow-up after DBS is hard to achieve).

Institution Dimension

- Quality standards in smaller DBS centers: Although in some countries (e.g., Switzerland) there is a discussion to ensure high case numbers per DBS center (Christen and Müller 2012), obviously many centers operate on only a few patients. However, we argue against fixed minimal case numbers for DBS centers, as determining the cutoff is arbitrary and other stereotactic interventions besides DBS (which have not been captured in our surveys) also account for the experience of a center. Nevertheless, it is important to find ways (e.g., binding guidelines) to ensure high quality also in smaller DBS centers, with regard not only to the surgical procedure, but also to patient information, patient selection, device programming, and pre- and postsurgical neurological and psychiatric assessment.
- Novel DBS indications planning: It is likely that DBS will become a bearer of hope for many psychiatric disorders—in particular, for depression, OCD, and Tourette's syndrome—for which known therapies have failed (e.g., recent studies estimate that more than 50% of patients suffering from depression may be treatment-resistant; Thomas et al. 2013). However, it will be important that the development of novel DBS indications is theory driven (i.e., based on a good understanding of the network in which one intervenes) and evidence based and not merely demand driven. In particular, the planning should involve the buildup of (optimally international) case registries, which should contain all clinical studies and individual treatment attempts for all novel DBS indications. Case registries are indispensable for preventing a publication-bias and its negative consequences, namely, faulty evaluations of therapies, flawed therapy recommendations, unpromising treatment attempts, and unneeded clinical studies (Müller and Christen 2011; Rabins et al. 2009; Schläpfer and Fins 2010; Woopen, Timmerman, and Kuhn 2012).
- Evidence-based evaluation of DBS for novel indications: For novel indications of DBS, an evidence-based evaluation is essential. Whenever possible, each novel indication should be investigated in clinical trials of the appropriate size and statistical power, requiring collaboration of centers. We support the demand of Fins and colleagues (2011) that the U.S. Congress and federal regulators should revisit the Food and Drug Administration (FDA) humanitarian device exemption that allows manufacturers to market a device under certain conditions without subjecting it to a clinical trial, for DBS for treating OCD. They argue convincingly that the humanitarian device exemption is misused for bypassing the rigors of clinical trials, since OCD is not an orphan but a prevalent condition, and that the current market-driven

regulatory strategy is detrimental to patient safety, scientific discovery, and research integrity.

- Capacity planning: Due to the rapid expansion of DBS indications, capacity planning in centers—at least for some countries—should become an issue soon. In some countries (e.g., Switzerland; Christen and Müller 2012) not all patients who are suitable for DBS may obtain this therapy. Unfortunately, there are almost no data available even for a disease like PD that allows for such planning (in particular, data that estimate the percentage of patients who suffer from a DBS indication and who are actually good DBS candidates, and data on the optimal case number per center to ensure both sufficient intervention quality—which speaks for higher case numbers per center—and optimal care and follow-up—which sets an upper limit for the number of patients operated per center). Therefore, health service research should put more resources into gaining information needed for DBS center capacity planning.
- Funding: A recent market study claims that the brain stimulation market "is expected to grow at a rapid pace and achieve a similar market size to the Global Cardiac Devices market" (Research and Markets 2013). Also according to our data, the experts see economic driving forces in the development of novel indications for DBS. Unfortunately, the current data do not allow assessing reliably the impact of private funding on DBS research. We recommend that papers on DBS (and other fields) should always disclose their funding source, independent of whether this source is private or public.

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Publication 3: Questioning the technology-development of DBS devices

Synopsis

Given the important ethical discussion of technological issues evidenced by the robust connection between the topics "hardware" and "ethics" (see publication 1), it was timely to critically address still insufficiently discussed issues. It also takes up the consideration outlined in the introduction that often it might be valuable to critically reflect on how the field is developing. Consequently, we felt it was time to pause for a moment in order to give room for critically reflecting on mainly unmet technological issues which at the end have ethical relevance for patients treated with DBS. The idea arose from discussions in the hospital mostly before and after surgeries for which I was always very welcomed. Consequently, we tried to make an argument for demanding technological improvement for the sake of patient safety and better future treatment.

By providing the reader with an exemplary case example which demonstrates the uncritical stance of many professionals in the field, we went on by outlining the often frustrating and time-consuming steps health-care professionals have to perform when having to choose by trial and error from thousands of stimulation parameter combinations in order to minimize side-effects. Often enough, unquestioned expert recommendations are used for every patient in clinical practice.

After discussing technological drawbacks and the missing of an automatic or remote report system of e.g. "red flags" for adequate patient oversight, we outline the difficulty of capturing clinical changes that are meaningful to patients and their families.

Next, we argue that by including an ethical framework, which is relevant for the neuroethical assessment of neuromodulatory interventions including beneficence and non-maleficence, one is able to structure the normative claim. Because device manufacturers can determine which experiments are worthwhile and which should be conducted and because it is unclear what happens when a device manufacturer goes out of business and equipment is no longer available, the industry would have to accept more responsibilities. Hence, we claim that the goals of technological innovation and patient welfare should be complementary and should involve device-makers and clinicians equally.

In summary, there is great need for sensitivity to the ethical duty to actively promote and demand technological advancements for the sake of minimizing undesirable complex side-effects.

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A critical reflection on the technological development of deep brain stimulation (DBS)

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Since the translational research findings of Benabid and colleagues which partly led to their seminal paper regarding the treatment of mainly tremor-dominant Parkinson patients through thalamic high-frequency-stimulation (HFS) in 1987, we still struggle with identifying a satisfactory mechanistic explanation of the underlying principles of deep brain stimulation (DBS). Furthermore, the technological advance of DBS devices (electrodes and implantable pulse generators, IPG's) has shown a distinct lack of dynamic progression. In light of this we argue that it is time to leave the paleolithic age and enter hellenistic times: the device-manufacturing industry and the medical community together should put more emphasis on advancing the technology rather than resting on their laurels.

Keywords: deep brain stimulation, technology, development, innovation, functional neurosurgery, stereotactic operation, ethics

INTRODUCTION

Early lesion studies in humans and translational preclinical research using laboratory models as well as concomitant early stimulation experiments, pharmacological treatment approaches with L-DOPA in 1968 and the identification of circuit physiology in the early 1980's have led to the development of neuromodulation techniques such as deep brain stimulation (DBS). In contrast to medication-based approaches, knowledge gained from DBS as both a probe and modulator of the underlying neural circuitry resulted in a new way of describing and understanding (neuro)-pathologies (top-down approach). Early stimulation experiments such as those using non-human primates (Kringelbach et al., 2010) were a glowing example of such development. However, we still struggle with explaining the mechanisms of action of DBS as Montgomery stated in his paper on logical pitfalls on DBS results and mechanisms of action (Montgomery, 2012). 2012 marked the 25th anniversary of modern DBS. Although DBS is being performed increasingly in centers worldwide, not much has changed regarding the integration of new technological know-how. This poses the distressing question of whether there is a duty to overcome this lack of progress. The general picture of an apparent arrested development does not at all light up when analyzing the approximately 40 years of emerging neurostimulation technologies which were adapted into therapies by neurosurgeons for different conditions during the 1970s (Gardner, 2013), besides early stimulation experiments on patients e.g., by Robert Heath and Jose Delgado. Compared to other technological advances in different domains ranging from consumer electronics to medical applications, the technological advance of DBS devices seems to be almost nonexistent.

Furthermore, DBS is at a critical turning point which is characterized by a subsequent collapse of the "last-resort" connotation DBS once had as a treatment for refractory disorders. Indeed, beyond broadening indications to younger patients with well-studied diseases, even questionable indications arise (Hariz, 2012). Is it legitimate to use the same electrodes and stimulation techniques in every region of the brain for movement or psychiatric disorders? And isn't it plausible that local anatomy may need different hardware/software combinations? Will old concepts of lesioning with new technologies, e.g., high-intensity focused ultrasound, replace DBS in some domains (Lipsman et al., 2013)? Is it possible that genetic and cell culture technologies could overrun the "gold standard" DBS for Parkinson's disease in the future (Lindvall, 2013)?

TECHNOLOGICAL DEVELOPMENTS: DIFFERENT CONTEXTS—SAME PATTERNS?

Figure 1 depicts some of the technological advances that have had applications both inside and outside the medical domain. For our purpose it is sufficient to state that the driving factors for technological evolution and innovation are the following:

1. reduction of size dimensions
2. increase of complexity and variability of tasks which can be executed

Lewis H. Morgan's stage model of social evolution involves the analysis of technological milestones and declares technological progress to be the primary factor driving the development of human civilization. On the basis of this model, there is the

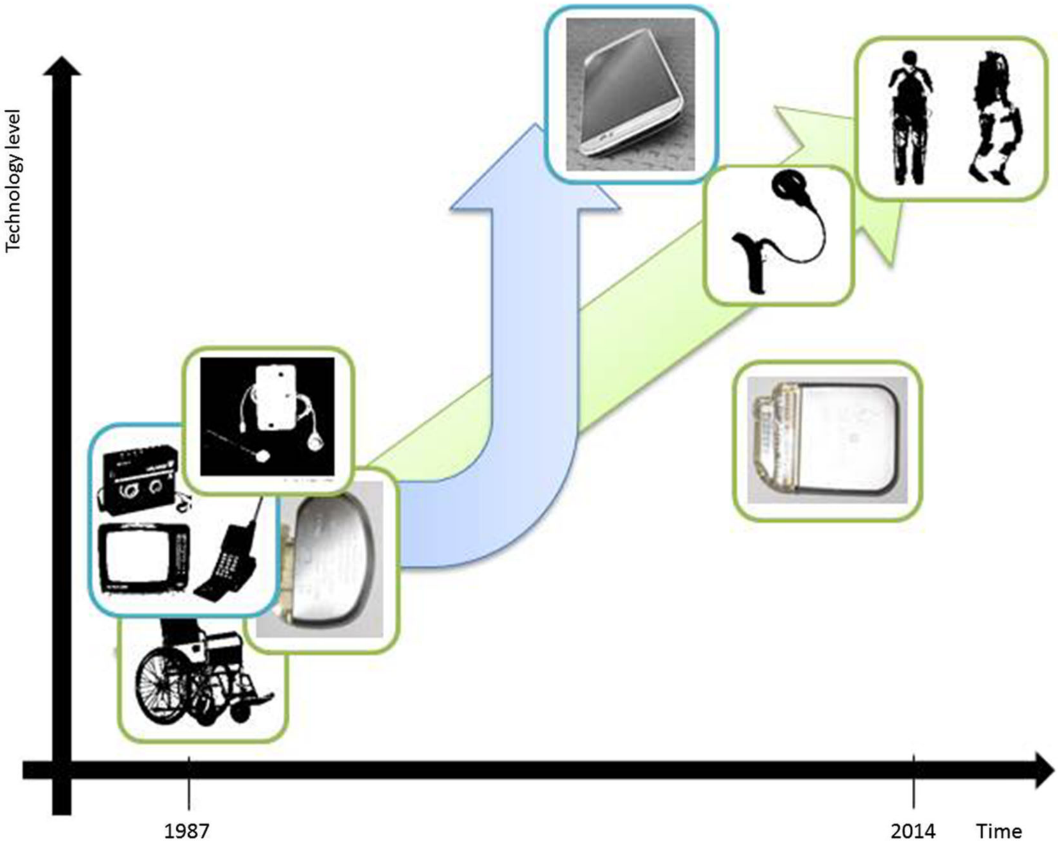

FIGURE 1 | Illustrative examples of technological developments in the past 25 years which refer to miniaturization aspects and ground-breaking change of technological complexity. Wheel chair bound patients could in the meanwhile benefit from the possibility of full mobilization due to an exoskeleton device (adapted from: http://www.medicalspro.com/manual_wheelchair.php, http://www.designboom.com/technology/elegs-exoskeleton-by-berkeley-bionics/). External devices of cochlear implants have become remarkably smaller (adapted from: http://www.enttoday.org/details/article/4550891/History_of_the_Cochlear_Implant.html, http://www.audiology.org.nz/Userfiles/Image/implant6_lge.jpg). Television, Walkman and Mobile Phone have become a single, extremely sophisticated multifunctional tool with wireless connections to other technical devices and integrating Internet (Smart-Phone). (adapted from: http://www.radiomuseum.org/r/waltham2_tele_star_4004.html, http://www.telegraph.co.uk/technology/5733286/Sony-Walkman-in-pictures.html?image=4, http://www.webdesignerdepot.com/2009/05/the-evolution-of-cell-phone-design-between-1983-2009/; IPG & mobile phone images used by courtesy of owner).

question of how to interpret our current evolutionary stage by focusing on DBS device advances (see **Figure 1**). Have we progressed beyond Morgan's savagery stage?

Pragmatically we think it is fair to say that in the context of DBS, neither (1) nor (2) have yet been satisfied (also see **Figure 1** for a direct, schematized visual comparison). The possibility of spatial steering brain stimulation (Martens et al., 2011; Hariz, 2014) or adaptive DBS (Little et al., 2014) barely rises at the horizon. Furthermore, settings are predetermined per electrode site and can be changed only in a very restricted way due to the missing feedback path (Eberle et al., 2011). Also it appears as if technological trends from neighboring disciplines (i.e., "technology-transfer" (Morlacchi and Nelson, 2011)), such as the gravitation-field sensor system in the context of spinal cord stimulation or nanotechnology have not in the least been adopted by the DBS industry. Currently, greater emphasis is put on the issue of MRI safety of DBS implants due to diagnostic highfield-MRI (Paek et al., 2013), which is increasingly being used in clinical work.

A THOUGHT-PROVOKING PIECE OF SURGICAL EVIDENCE

Results of randomized controlled trials have just recently been published without major differences regarding outcome of STN-DBS vs. GPi-DBS (Weaver et al., 2012; Odekerken et al., 2013). **Figure 2** depicts the desperate search and use of the newest technology available for treating a patient with Parkinson's disease. Both physician and patient were willing to try the best treatment possible for alleviating the symptoms of this disabling disease. The X-ray images were acquired in 2009 before exchange of the implantable pulse generators (IPGs) connected to the STN (subthalamic nucleus) electrodes. One could speculate that a change to a more sophisticated technological system in GPi (globus pallidus internus) stimulation could have served the purpose of inducing a therapeutic effect without undergoing additive stereotactic surgery. Those

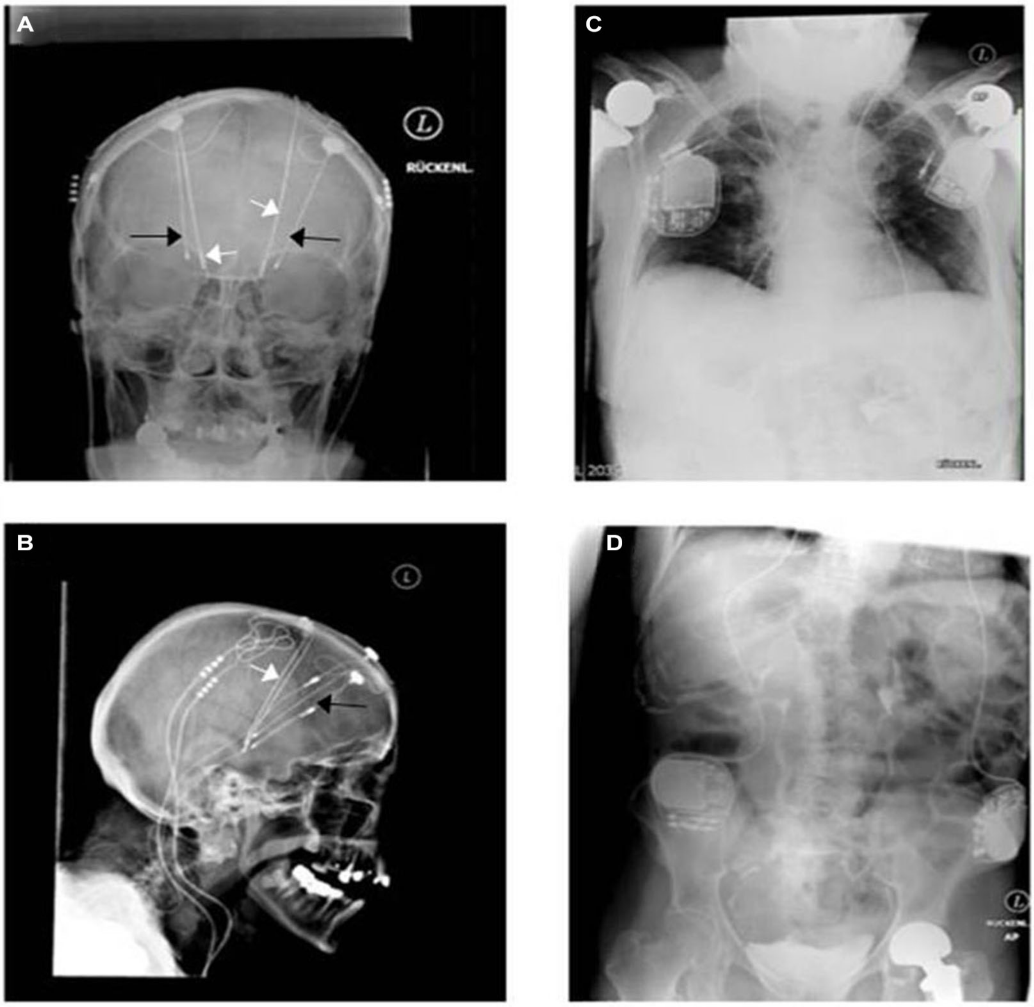

FIGURE 2 | A unique witness of DBS history. Bilateral monopolar electrodes were implanted within the internal globus pallidus (GPi) in 1998 in a patient having suffered from typical Parkinson's disease since 1984. Predominant disabling dyskinesia improved significantly afterwards (black arrows: more lateral in **(A)** and more anterior in **(B)**). Because of re-emerging motor fluctuations without further optimization possibilities of the monopolar GPi electrodes (probably side effects), bilateral quadripolar electrodes (white arrows) were then implanted within the STN in 2001 accounting finally for four intracerebral electrodes and four pulse generators **(C,D)**. The patient profited for around 3 years before developing late stage symptoms, like frequent falls, voice alteration, On-dystonia in her lower extremities and cognitive decline. The two GPi generators were explanted in 2009 as additional beneficial effects were not seen.

images unmask the hopeful will to change treatment in regard to hardware and target without having understood the failure of the monopolar GPi stimulation in this patient. The transition from mono- to quadripolar electrodes still remains the maximum of technological progress today. In daily clinical work, there is a subliminal frustration on the imbalance of having more than 10,000 programming possibilities, e.g., frequency, pulse width and amplitude, without being able to optimize stimulation for the individual patient (Volkmann et al., 2006; Ricchi et al., 2012). Instead, expert recommendations remain the evidential basis of setting parameters. Regarding multiple joint prostheses and four IPG's, this patient has reached nearly the limit of medical implant costs.

TECHNOLOGICAL CONSIDERATIONS

The recent advances of increased magnetic field strength observed in MRI-system technology should ultimately lead to an improvement in the accuracy of electrode positioning. This is particularly important given the high interindividual anatomical variability of structures such as the STN, because personalized, image-based targeting provides higher accuracy than atlas-oriented targeting (Ashkan et al., 2007). Moreover, Zaidel et al. (2010) showed optimal clinical efficacy by determining local electrophysiological parameters characterized by increased β-oscillatory activity on multi-unit recordings rather than by pure anatomical analysis.

Today, the impossibility of detecting specific alterations in underlying brain activity depending on the condition being treated is a major limitation. Do we pay tribute to extremely complicated homeostasis patterns of a billion years of evolution, e.g., circadian neuroendocrine interaction and electrochemical networks? Currently, IPGs can be programmed through modifying frequency, pulse width, current output (amplitude), interleaved mode (Baumann et al., 2012) between contacts and limited possibilities of groups/cycling modes. In routine clinical practice, the physician usually takes "standard" programs known from the literature. In case of side effects of medication and stimulation interaction in the variable disease patterns, "trial and error" within thousands of programming possibilities can be frustrating, extremely time-consuming and may require hospitalization of "difficult" patients (Volkmann et al., 2006; Hariz, 2012). Steering the electrical current and granting MRI compatibility are recent and important developments to solve the problem of side effects, energy consumption and harmless hardware-tissue interaction (Hariz, 2014). Given that the brain uses dual-mode communication and feedback strategies, an effective treatment needs to detect and return both real-time monitoring of chemical neurotransmitter release levels as well as electrical firing patterns (Rosin et al., 2011)—in other words, closed loop self-regulatory systems (Grahn et al., 2014). One of these systems is currently under investigation at multiple centers worldwide without any information, yet on future efficacy or availability. The advances of real-time, instantaneous neurochemical and electrophysiological sensing combined with feedback-guided anticipatory adjustment and sophisticated electrode (lead) design (Arcot Desai et al., 2014; Hariz, 2014; Kent and Grill, 2014) could lead to a fully integrated, small and high precision, low-power circuit supporting a wireless neuromonitoring and neuromodulation system (Shah et al., 2010). Hence, avoiding thick, unlabeled cables and clumpy IPGs would reduce acute and long-term morbidity as hardware complications still remain frequent adverse events in DBS surgery in many centers (Hamani and Lozano, 2006).

Additionally, there is a lack of monitoring and integrating disease symptoms together with general health and activity status of the patients. There is no automatic or remote report system, e.g., of "red flags" of symptoms or hardware-related problems, not even for precise battery life duration.

We argue therefore that the time has come to focus on advancing the DBS system in terms of technological properties to better meet individual patient needs, leading to more effective symptom control, improved patient quality of life and reduced healthcare costs.

Given the importance of DBS, the lack of biomarkers for many complex conditions and the associated need for a critical and objective pre- and post-DBS therapy evaluation, we argue that we should emphasize improving means for a holistic evaluation of patient's clinical status. As Gardner (2013) brought to the fore the decisive role of the invention of a (synthetic) UPDRS rating scale for the emergence of DBS, we also have a duty to critically question whether the creation of such an objective numerical variable in order to have a basis for comparing pre-and post-stimulation effects fully embraces the patient and results in improvement of symptoms. Gardner further states: "Thus while such a tool may generate the necessary "objective evidence" to legitimate the intervention and enable device manufacturers to market their device, it may not be capturing clinical changes that are meaningful to patients and their families" (Gardner, 2013). Thus, quantified rating scale scores have to be complemented by qualitative measures (Bagby et al., 2004).

ECONOMIC CONSIDERATIONS

Of course, medical products are under stricter regulatory processes than consumer goods, and doctors or patients are not simple consumers. To the best of our knowledge, one single company held the monopoly for DBS application systems for almost 20 years. Even after the introduction of two other key companies, besides newly emerging vendors highlighted in a recent market study (Global Deep Brain Stimulator Market 2012–2016),[1] there was no ground-breaking new technological development. Not more than minor changes in programming possibilities, lead and fixation design, and battery properties have occurred. This is problematic since we find ourselves in a context of severe diseases which depend on innovative treatment options. The lack of favorable (see Hashmi, 2013) competition for product-innovation for developing safer and more effective neuromodulation techniques stands in marked contrast to the situation of other technological domains outside the medical field, such as the mobile phone or automobile industry. Here we face a highly dynamic progression of consumer-oriented new developments. In other, more competitive domains within medicine, such as orthopaedic surgery/applications, a more innovative landscape can be observed. A lack of competition may be one reason why we are confronted with a shortage of technological progression in the DBS field. By looking at the economic literature, and by keeping in mind that the health-economic sector is different, one could argue that more product market competition can under certain circumstances increase product-innovation (Aghion et al., 1999, 2009; Aghion and Griffith, 2005; Hashmi, 2013; Roper et al., 2013).

In the DBS context, it is unclear why we do not face a pronounced conflict between attending physicians and industry regarding differing claims. Possibly there is not enough demand (supply-and-demand situation) verbalized by the medical establishment which could explain a lack of innovation potentially due to daily work-intensity and time pressure, regulatory hurdles, investment return considerations, installed base effects, a lack of knowledge-transfer from basic science to users in clinic or a low level of sensibility to grasp the responsibility to strive for more benefit to the patient.

One could potentially identify a subliminal tendency towards investing in other indications, thereby increasing the number of implants instead of improving quality.

ETHICAL CONSIDERATIONS

We argue that there is a multidimensional obligation to promote innovation which should include all agents involved in the process of helping patients in need. We restrict ourselves to the two domains already highlighted above, namely the medical community and the medical device industry. Those domains

[1] http://www.researchandmarkets.com/reports/2538063/

should both promote innovation since they have complementary rather than competing goals. In the following, we focus briefly on the medical community on the one hand and more extensively by the use of a framework-based argumentation on the medical device industry on the other.

It appears that the medical establishment has failed to build on the dynamic treatment breakthroughs of the past due to overconfidence and a lack of vision. The initial clinical efficacy in resolving some symptoms obscured the once broadly heralded, noble aspirations of gaining deeper understanding of DBS. Even though the subsequent unraveling of side effects could have driven clinicians to obtain deeper scientific knowledge as well as to optimize treatment, this unfortunately was not pursued with the required vigor.

We believe that it is therefore time to include some ethical reflection in the debate. One could argue that industry and the medical community both have a duty to invest more in technological advances by concomitantly ensuring that treatments are safe and effective (Hofbauer et al., 2013). Generally more emphasis should be put on basic scientific advances (Hamani and Temel, 2012), thereby reaching a level of development which in the end will, as a manifestation of a sensitive pleading for the centrality of patients, help those most in need. Also the question of an ethical responsibility to strive for the best and latest technology for the treatment of one of our most sheltered organs, our brain, should be discussed.

An ethical framework is needed to make this normative claim more transparent and more systematically structured. We believe that interposing some normative considerations may have beneficial effects in terms of sensitizing the community. This could be a starting point for an eclectic and multifaceted normative discussion. Moreover, such a framework is necessary to guide innovation within the field of DBS. In order to make a normative claim such as the duty or responsibility to promote technological advance, one may pursue this idea by making use of an already established ethical framework such as the one provided by Beauchamp and Childress (2013), thereby analyzing the effects of technological development on primary ethically relevant parameters. We have chosen this particular framework as a starting point for normative reflection because of its established and wide use within the clinical context. It incorporates two core bioethical principles, namely "*primum non nocere*" *("First, Do No Harm")*, reflected in the duty of nonmaleficence and beneficence, which could be described as the duty to promote the good of others. Regarding the need for and further development of neuromodulating devices, the principle of beneficence is especially ethically relevant. We believe that it is important to incorporate the values reflected in these principles into the context of industry. For one could argue that patients' well-being may be positively affected by the implementation of technological innovation. Beneficence and nonmaleficence apply not only to the medical domain but also to that of industry and need to be balanced with the economics of the medical device industry and the need for companies to survive.

The application of these principles means that the ethical justification of any technological advance in neuromodulation depends on whether it is beneficial for patients and improves their well-being. As stated above, we argue that ethical considerations require that all stakeholders should be involved in the discussion. Accordingly, a duty to promote technological advance should not be restricted to the medical domain but also should be radially projected in order to positively affect all agents involved. If we genuinely care for the patient's wellbeing, then the principle of beneficence should not only apply to the medical context but should have the power to transcend contextual barriers.

The goals of technological innovation and patient welfare should be complementary. Device-makers funding DBS clinical trials have an obvious interest in proving that their product can modulate neural circuits. Yet this has the potential to create a conflict of interest for researchers wanting to know how DBS affects the brain and mind of subjects if the manufacturer influences the design of the trial and the interpretation of the results. The potential for conflict is greater when the researcher has invested in such a company. Policies must be in place to prevent or at least reduce the probability of this conflict by ensuring the scientific integrity of clinical trials and that testing DBS is consistent with the interests of patients in experiencing symptom relief and improved quality of life. Ultimately, patient welfare should be the main impetus of any duty of innovation to produce more advanced neuromodulating devices (Fins and Schiff, 2010; Fins et al., 2011).

In our discussion of beneficence, we identified one pertinent principle which we thought to be easily accessible as well as used in practice. But because it is beyond the scope of this paper, we refrain from elaborating on the critical steps of balancing and weighing different values against each other. There might of course be other issues that potentially outweigh a duty of innovation under certain circumstances.

Moreover, there is a need for interdisciplinary exchange between and among representatives of patient organizations, industry, basic science, medicine and ethics in order to shape the future of DBS. A recent interdisciplinary, international forum ("brains in dialogue", BID project)[2] trying to foster this dialogue was unfortunately closed.

CONCLUSION

DBS is an established therapeutic intervention and has recently provided hope for many patient groups including but not limited to movement disorders. Significant innovation in the field of DBS has mainly been reflected by introducing novel indications, rather than advanced technologies. We still lack a mechanistic explanation of the underlying processes involved. In turn, one has to acknowledge that the limited understanding of brain functions (bottom-up approach) poses a critical barrier to innovation. Deeper insight is crucial to further advance DBS systems towards intelligent, self-regulating closed-loop devices in combination with miniaturization and MRI-compatibility of hardware, sophisticated electrodes and programming possibilities. Furthermore, especially in the case of new indications, international joint

[2]http://www.neuromedia.eu/NewsData.aspx?IdNews=1325&IdType=296&type=Actual

meetings should include preclinical translational researchers as well as ethicists, recognized patient organizations, engineers and healthcare providers in neurology, neurosurgery and psychiatry for the translation of technological advances in order to create consensus of future directions of development and to improve outcomes of established indications. This consensus could be addressed to regulatory bodies for a representative impact. Finally, there is a greater need for sensitivity to the ethical duty to actively promote and demand technological advancement in neuromodulation.

AUTHOR'S CONTRIBUTIONS

Christian Ineichen and Oguzkan Sürücü wrote the paper, Walter Glannon, Christian R. Baumann and Yasin Temel provided valuable feedback and substantially contributed to this work during the process of writing. Christian Ineichen furthermore confirms that he has final responsibility for the decision to submit for publication.

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Publication 4: Developing an instrument for measuring complex changes

Synopsis

As outlined in the introduction, mental capacities and moral competencies (among others) of the patient have high ethical relevance in the context of autonomy. Hence, by incorporating the previously described moral-psychological framework of Moral Intelligence (see introduction), we emphasize the role of psychological skills required for moral behaviour. In this paper, we describe the construction of an instrument for measuring moral sensitivity. As outlined in the introduction, the idea of the instrument construction was the development of a not too fine-grained but also not too general tool which can be adapted in order to allow researchers to e.g. investigate moral-behavioural and personality-related changes post-lead implantation and stimulation.

More precisely, the instrument is based on the construct "value sensitivity" which denotes to the ability to recognize (moral) issues when they arise in practice. If interested in assessing complex behavioural and personality-related changes post-operatively, the need of psychologically informed instruments which include explicit and implicit measures and which are based on recent moral-psychological insights of human behaviour is apparent. Hence, we developed an instrument for assessing value sensitivity and complemented this research with instrument validation by comparing nursing professionals with hospital managers.

In accordance with our hypotheses, the group comparison demonstrates the expected differences in value-sensitivity regarding moral and non-moral related values of the two groups: We find that nursing professionals recognize and ascribe importance to principle-related issues more than professionals from hospital management. The latter are more likely to recognize and ascribed more importance to strategy-related issues. Hence, the instrument displays adequate discriminatory power.

In a next step, the goal will be to adapt the instrument for assessing potential changes in patient sensitivities postoperatively related to relevant values for this domain. This will allow us to potentially identify changes in patients' perceptions which are meaningful for the patients and their relatives and which might explain some of the difficulties they face postoperatively when witnessing nuanced changes in personality and or in the expression of behavioural acts partly responsible for conflicting outcome interpretations and satisfaction gaps.

Submission for BMC Medical Ethics – Title Page

Measuring Moral Sensitivity in Medicine – Means and Justification

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Submission for BMC Medical Ethics – Manuscript

Abstract (278 words)

Background: *Moral sensitivity – the ability to recognize moral issues when they arise in practice – is an indispensable competence for medical practitioners to enter decision-making processes related to ethical questions. However, the psychological competence of moral sensitivity is seldom an explicit subject in the training of medical professionals. In this contribution, we outline the concept of moral sensitivity in medicine, we propose an instrument that measures moral sensitivity, and we investigate risks and benefits of improving moral sensitivity in medicine.*

Methods: *We developed an instrument for assessing the sensitivity for three value groups (moral-related values, values related to the principles of biomedical ethics, strategy-related values) in a four step procedure: 1) value identification (n = 317); 2) value representation (n=317); 3) vignette construction and quality evaluation (n=37); and 4) instrument validation by comparing nursing professionals with hospital managers (n=48). This empirical analysis was complemented by literature research on moral sensitivity in medicine and related fields and with normative considerations.*

Results: *We find that nursing professionals recognize and ascribe importance to principle-related issues more than professionals from hospital management. The latter are more likely to recognize and ascribed more importance to strategy-related issues.*

Conclusions: *These hypothesis-driven results demonstrate the discriminatory power of our newly developed instrument, which makes it useful not only for health care professionals in practice but for students and people working in the clinical context as well. Finally, we provide a broad overview of normative questions associated with the performed research. We discuss the practical significance of moral sensitivity in medicine and the value of improving it. We also delve deeper into potential risks that may be associated with a moral-sensitivity-assessment instrument and attempts to improve it.*

Keywords: Moral Sensitivity; Ethical Sensitivity; Moral Values; Moral Competences; Medical Ethics Training

1. Introduction

In medicine, there is a need to emphasize the psychological prerequisites for clinical acting [1]. Generally, psychological moral competencies of medical professionals are rarely assessed, and there are hardly any instruments that are appropriate to measure such competencies. One such relevant competence is moral sensitivity, a prerequisite for moral decision-making and behavior. In this contribution, we investigate means and justifications for developing competences that are required to implement virtuous behavior in clinical practice [2, 3]. Based on previous research (identification and characterization of context specific values [4]), we aimed at developing an instrument which measures moral sensitivity in medicine. The instrument is aimed at supporting medical professionals and their patients by empowering healthcare practitioners to recognize dilemmas when they arise in practice. As it is not clear whether enhancing moral sensitivity per se is positive under all circumstances, we address the need to explore the normative implications resulting from the proposed research. With this work, we outline the procedural steps necessary for the development of the instrument. Next, we describe the validation of the instrument by means of a group comparison. Finally, we complement the work by a broad normative reflection with an emphasis on potential risks and benefits of improving moral sensibility.

1.1. The concept of moral sensitivity

Moral sensitivity (also referred to as moral awareness or ethical sensitivity/sensibility) is commonly defined as the ability to recognize moral issues when they arise in practice [3, 5 - 8, see also 9 or 10 for reviews on varying definitions of the construct]. More precisely, moral sensitivity incorporates both the ability to recognize moral issues in a morally ambiguous situation and the ascription of importance to these same issues [11]. It includes being responsive to the needs of others in addition to anticipating whether a course of action can harm or help others or whether it violates internalized moral standards or codes of conduct. In line with this conceptualization, we adopt a definition of moral sensitivity that includes both the recognition and the ascription of importance to moral issues. Accordingly, moral sensitivity is proposed to cover both, an intuitive- (quick, reflexive recognition of a morally relevant aspect in a situation) and a deliberative process (vectored attentiveness to morally relevant aspects).

Lack of moral sensitivity – also called moral blindness – is likely to have far-reaching consequences. Researchers found that “morally blind” people can act with the best of intentions but behave in contradiction to their own values and principles, without being aware of it [12]. If the moral issues at stake are not identified, no moral problem will exist for the individual and therefore there will be no need to enter into a moral problem-solving phase [13]. Thus, it is obvious that without a certain moral awareness, there is no reason to question one’s or other’s behaviors from a moral point of view. Consequently, without moral sensitivity, professionals may not be able to appropriately recognize, interpret and respond to the concerns of patients and their relatives.

Although many researchers agree on categorizing moral sensitivity as a prerequisite for the initiation of moral decision making (e.g. [6, 13]), past research has focused more on the development of instruments for measuring the latter while largely neglecting the former [14]. The Dental Ethical Sensitivity Test (DEST) by Bebeau and Rest (1982) [15] is the oldest measure of moral sensitivity and was created to measure individuals’ ability to identify ethical issues and deviations from professional codes of ethics in dental practice. More recent attempts focus on the measurement of moral sensitivity in the business domain (e.g., in accounting or business situations). In 2007, Jordan [9] provided a comprehensive review and critical evaluation of the available measurements, pointing out that there is still a great need for validated measures of moral sensitivity (see also [16] for an emphasis of the medical context). A concise evaluation of those tests indicates that current instruments fall short regarding several aspects (see also [9]). For example, they often lack an evaluation based on criteria of diagnostic test theory. Our research project aims at developing an instrument for the measure of moral sensitivity which overcomes such pitfalls and is part of a comprehensive theory of moral intelligence [3].

We will expand the concept of moral sensitivity by considering a broader spectrum of values. The reason for this is that the current research on moral sensitivity focuses on values whose relation to morality is undisputed both from a theoretical perspective (i.e., they are discussed as prototypical moral values in the ethics literature) and based on empirical findings (i.e., people consider those values to be *moral* values). Examples include benevolence, honesty, or fairness. However, in professional contexts, other values may be relevant as well, although they may not be perceived as moral values (e.g. cost-effectiveness or reputation). By the term ‘value’ we refer to stable beliefs about desirable states or conducts of behavior, which serve as general normative standards to judge and justify actions not necessarily related to ethics [17]. Therefore, we suggest that an assessment of moral sensitivity should include values that are not intuitively perceived as moral but that refer to legitimate claims within the specified domain. By “domain”, we refer to any social sector, for example, professional fields such as medicine or business, associated with a specific set of values that are considered to be important in that sector. In the following, we therefore refer to the notion of “value sensitivity”. Based on previous research [4], value sensitivity in the research context of medicine is composed of three subcomponents: sensitivity for moral-related, principle-related and strategy-related values.

1.2. The relevance of moral sensitivity in medicine

The medical domain exceptionally challenges ones’ moral competencies because of numerous problems in that domain. These include actions under time pressure, inclusion of high-level moral values (e.g. non-maleficence) and dilemmas involving numerous stakeholders apart from structural barriers. Much of the controversial discussion focuses on codes of conduct. Some authors certify that these codes have only minor impacts on daily practice [18] and found that nurses evaluate them as being of little use [19]. Some studies investigating the success of teaching medical ethics even observed that the student's moral sensitivity diminished over the course [20]. This result may indicate that traditional teaching strategies tend to overlook the key competence of recognizing dilemmatic moral aspects in ambiguous clinical situations. In the past, authors such as Kleinmann complained about the neglect to promote psychological competences in teaching programs [1]. Consequently, the question of which specific psychological abilities have to be trained to realize such competency has not been adequately emphasized. Accordingly, we point out that moral behavior is not solely reflected in knowledge about ethical theories but also by paying attention to the psychological conditions of ones' own moral ability. Both aspects should be included in medical education.

If moral behavior rests on moral competencies, the need for tools to measure the baseline status with the possibility of training such skills becomes an important undertaking [21]. We suggest that one way of supporting health care professionals' training is to allow them to learn about their individual strengths and weaknesses with respect to their own moral sensitivity. In medicine, it is important to be able to obtain a swift recognition of which values are involved in a particular situation and which stakeholders could be affected by the ethical decision (e.g. patient, physician, or close relatives). Therefore, we consider it as an imperative to holistically integrate the insights of recent moral (psychological) research about the conditions of human moral ability into medicine in general and in the process of education of medical professionals in particular. Potential applications of our model are: (1) as a diagnostic tool for medical professionals in order to mirror possible strengths and weaknesses, (2) as an educational tool in the context of medical school and (3) as an instrument for advanced training of individuals, who work, for example, as clinical ethicists.

Interestingly, previous research on moral sensitivity indicates that there are differences between professions and the gender of those who work in these professions [11, 22 - 29]. Jordan [9], for example, demonstrated that business managers are less likely to detect moral-related dimensions than academics when providing them with morally ambiguous business situations. Furthermore, Harenski and collegues [29] have emphasized gender differences in the context of moral sensitivity. Specifically, females show increased care-based processing.

Yet, the body of evidence that people differ quite substantially in terms of moral sensitivity and that this capacity is related to moral behavior makes moral sensitivity a subject of normative inquiry. In this paper, we wish to extend this work by providing a broad overview of key normative issues, such as the practical significance of moral sensitivity in medicine. We also discuss advantages and disadvantages in promoting and assessing this capacity.

2. Developing an instrument for measuring value sensitivity.

As outlined in the last paragraph of section 1.1., we embed moral sensitivity into the broader concept of value sensitivity. We performed steps towards developing an instrument designed to assess value sensitivity. First, based on previous research we gained empirical evidence for a domain-specific value selection as well as insights into what extent the values are perceived as moral values (step1: value identification). Notably, domain-specificity may include the possibility that the perceived morality of values differ between domains. Thus, in business compared to medicine, it is likely that other values are deemed important and shared values might cluster differently. This relates to the work of Bebeau and Thoma [30] who used the term “intermediate ethical constructs” to refer to profession-specific concepts within a given domain (e.g. in medicine: professional autonomy, informed consent, privacy). Second, we obtained representative statements which were used as stimulus material instead of naming the values explicitly (step 2: value representation). Third, we developed and validated morally ambiguous vignettes characteristic of the clinical context (step 3: vignette construction and selection). These three steps are described below in Sections 2.1 to 2.3. In paragraph 3, we describe the validation of the instrument by means of a group comparison.

The functioning of the instrument is summarized as follows (see infographic below): Using a vignette-based approach, the instrument has been designed to present people with morally ambiguous situational descriptions and to investigate 1) which values they are more or less likely to identify and 2) which values they consider important within the presented scenario. After vignette presentation, respondents were provided with a list of value-related statements (items, see step 2: value representation) among which they could choose. The extent to which respondents to several vignettes choose more moral-related values and rank them as more important relative to other categories of values is indicative for value sensitivity.

All studies in this research were conducted in accordance with the ethical review processes of the University of Zurich and with the "Ethical Guidelines for Psychologists of the Swiss Society for Psychology" (http://www.ssp-sgp.ch/06_pdf/ersgp2003.pdf) and were analyzed using the software package SPSS Version 23.

2.1. Step 1: value identification:

A general challenge when assessing moral sensitivity is the identification of relevant values for the domain under consideration. There is also the challenge of investigating to what extent these values are perceived as moral- or non-moral in order to develop balanced vignettes that reflect the moral ambiguity of a particular situation (see step 3). Therefore, the first step of the construction phase involves the investigation of the "moral foundation" relevant for the medical context.

2.1.1. Participants and Procedures

In order to examine which values are perceived as being examples of moral or other categories of values, a sample of medical students and professionals (n = 317; 54.3% females, mean age: 26.6) was asked to evaluate a number of values along four moral-related dimensions (for more details see [4]).

2.1.2. Results: value identification

The main outcome involved an empirically informed classification of distinct value-clusters along the moral vs. strategic (non-moral) continuum. Based on that, we were able to classify 11 values in three clusters: A first cluster (the "general morality-related cluster") was composed of the values of responsibility, honesty, loyalty and respect. These values obtained higher ratings on all moral-related dimensions, suggesting that they were perceived as examples of moral values. A second cluster ("strategy-related cluster") included the values performance, cost-efficiency and reputation. These values received consistently low ratings on all dimensions, suggesting that they were perceived as unrelated to moral aspects. Interestingly, we found that all values associated with the principles of biomedical ethics [31] – non-maleficence, justice, beneficence (in our context: care, for an explanation see [4]) and autonomy – formed a separate, third cluster ("principle-related cluster"). Based on the ratings, those values were between the other two clusters, yet closer to the moral than to the strategy-related value-cluster. Due to their importance in training medical personnel in biomedical ethics, this group was included in the instrument development as well. (For an in-depth description of the rationale for selecting values and their categorization into three groups, see [4]). Notably, some of the values (care, non-maleficence, loyalty, justice) relate to Haidt's moral foundations [32], although not all of them received ratings such that they have been classified in the general morality-related cluster.

2.2. Step 2: value representation:

Since our assessment of individuals' sensitivity to particular categories of values is based on the kind of value-related items that people consider relevant for the dilemma contained in the vignette, another challenge was to minimize the flaw of provoking socially desirable answers. Such a risk may be likely when values (such as honesty, fairness, and the like) are explicitly named in an item. A central issue was therefore to avoid naming the value in the wording of the items, such that the presentation of stimulus material to subjects did not guide participants to attend to ethical (or related) issues. The method used here was designed to minimize this flaw. Furthermore, providing only a single value term involves the risk that the meaning of the term is under-determined for the participant. In step 2 of the construction phase, we therefore wanted to obtain adequate descriptions of such values, preferably by using short statements for each value describing typical behavioral manifestations of the corresponding value. The statements had to fulfill the criteria (1) of inherent and related normativity (i.e. they had to be similar to the values they describe), (2) they should incorporate the perspectives of different stakeholders (patients, doctors; hospitals and care-centers), (3) they should incorporate different behavioral actions which match the values, and (4) finally they should be synonymous, as opposed to explicitly naming the value at stake. In order to present material for quality-assessment, we developed four statements for each value.

2.2.1. Participants and Procedures

The statements were presented in randomized order. Participants (same sample as in step 1, n = 317) quality-checked each statement using a bipolar 6-point Likert scale ranging from 1 (not representative at all) to 6 (very representative). In order to effectively avoid socially desirable answer tendencies, we included one distractor-statement in every set of statements. For example, one distractor-statement describing “performance” was included in a set of four statements describing “autonomy”. Accordingly, participants were presented with five statements per value. As distractors, we used preliminary developed but superfluous value statements.

2.2.2. Results: value representation

In order to obtain representative statements for each value, we calculated the mean of each statement based on the Likert scale evaluation of participants (due to the vast number of statements, the whole list of statements is presented in Table 1a/1b in Supplementary Materials only). Statements resembled the following structure: For care we used "A physician or a caregiver should provide assistance to patients who cannot help themselves". A high mean value indicated high representativeness. Statements were selected only if their mean value was above 4.5. Six out of 44 statements did not meet this criterion and were excluded for step 3 and 4. After representativeness-testing, we retrieved two to three statements for each value which could be integrated as stimulus material into our instrument.

Most distractors achieved the lowest mean-values for each value-group (9 of 11; see Supplementary Materials Table 2: Distractor analysis). In one case including the value "responsibility" where the distractor achieved a higher mean value, the distractor was inappropriately chosen due to excessive semantic overlap (distractor for responsibility was "care"). We also conducted t-tests for verifying statistical significant differences between distractors and the mean-wise lowest statement for every value. Results demonstrated a statistically significant effect on 8 of the 11 comparisons (see Supplementary Materials Table 2: Distractor analysis).

2.3. Step 3: vignette construction and selection:

Step 3 consisted of constructing vignettes that describe conflict situations that are relevant for the medical context. Based on a literature research and interviews with medical experts in Switzerland, we developed 12 vignettes of approximately equal length, morally ambiguous content and the integration of multiple stakeholders. Prior to study inclusion for quality assessment, these vignettes were reviewed by external experts from medical ethics.

2.3.1. Participants and Procedures

After assessing demographic information (gender, age, field of study, number of completed semesters) and information about participants' work experience in medicine (whether they have work experience, and what kind of experience), participants (n = 37; 78.4% females, mean age M =

25.9 years, 62% medical students, 16% from nursing school, 45.9% reported to have work experience) were instructed to put themselves in the role of a clinical expert in charge who is partly involved as a committee member of a clinical expert-group. They were told that currently, there were six cases (2 cohorts, 6 cases/vignettes per cohort) to be discussed during the next committee meeting. In this way, the participants were primed in a similar way as in the main study (see step 4, below). Then, the participants were asked to evaluate the vignettes according to the following quality criteria: (1) comprehensibility, (2) required level of expert-knowledge, (3) relation to reality, (4) extent of achievement-oriented, reputation-related or economic-related content and (5) extent of moral-related or social-oriented content by the use of a bipolar 5-point-Likert scale. (4) and (5) were assessed as quality criteria for moral ambiguity (i.e. balanced involvement of moral and strategic aspects in the vignette, [6]). Moral ambiguity is a vital prerequisite of vignettes to prevent biased responses. The vignettes were all between 137 and 202 words long, developed and preselected by two writers and one external reviewer and written based on the results of steps 1 and 2.

2.3.2. Results: vignette construction and selection

We calculated the means of the 5-point-Likert scale evaluations regarding quality and moral ambiguity of the vignettes (the results of the descriptive analysis are given in Table 1). Vignettes were selected for further review if (1) comprehensibility was achieved (i.e. mean values ≤ 2.5), if (2) the requirement of expert-knowledge was moderate (i.e. mean values between 1.5 and 3.5), if (3) relation to reality was high (i.e. mean values < 2.5) and if (4) the vignettes incorporated both strategic as well as moral aspects but not to a very obvious but rather ambiguous extent (i.e. mean values < 4.5).

A pivotal criterion was the balance between strategic and moral elements in each vignette (i.e. moral ambiguity). To test moral ambiguity and based on the average rating (M_{Moral}, $M_{Strategic}$), we conducted single t-Tests to test for dissimilarity. If means differed significantly, the vignette was excluded. Moreover, a Shapiro-Wilk test was conducted and yielded a significant result highlighting non-normality of the data due to the low sample sizes of the preselected vignettes. Therefore, a non-parametric Wilcoxon signed-rank test was executed. All results of the single t-Tests were confirmed. Five vignettes (number 1, 3, 5, 6 and 7, see Table 1) fulfilled the necessary criteria and were included as stimulus material in our instrument. The five chosen vignettes involved work-place problems within a clinic (V1 & V3), conflict within a nursing home (V5) and two vignettes including research issues in neurology (V6 & V7). The results are described for the selected vignettes only (the selected vignettes are displayed in Supplementary Materials).

TABLE 1 ABOUT HERE PLEASE

As mentioned earlier, the previously described three steps encompassed the first phase in the development of our value-sensitivity measure. In what follows, we advance this work by providing a first validity test of this measure.

3. Testing the validity of the value-sensitivity measure

3.1 Hypothesis generation for expected group differences

In our final step, we aimed at demonstrating the validity of the measure by making use of a group comparison.

Hypothesis generation for the group comparison included some theoretical concepts: Regarding the reasons for inter-individual differences in perceiving moral issues in ambiguous situations, contemporary research predominately refers to social cognition theory (e.g., [33]) positing that individuals hold cognitive schemas (i.e. cognitive representations) depending on socialization. These models also imply that priming (activating a concept by providing external stimuli such as a word, a picture or an object; [34]) of a representation would foster its future activation by increasing its accessibility. Consistent with this, a substantial body of research clearly demonstrated that (consciously or subconsciously) primed information guide attention, encoding and the categorization of the situation by making concepts temporarily more accessible (for an overview see [35 – 37]).

Some schemas are chronically accessible in that they become automatically and habitually activated [36, 38]. Examples of chronic accessible representations are strong attitudes and deeply held values, beliefs or traits that are central to one's identity or culture. In line with this, moral standards or values are acknowledged as moral schemas that vary in their accessibility [2, 11, 39]. Hence, individuals whose moral schemas are more accessible or even chronically accessible are expected to be more likely to direct attention more or less automatically and swiftly to moral issues. For example, Jordan [11] has argued that business managers are less likely to detect moral-related dimensions than academics, because business managers have business rather than moral schemas guiding their attention and information processing more dominantly. Overall, researchers in moral psychology consistently conceive the activation and accessibility of moral schemas as crucial conditions of demonstrating moral sensitivity [9, 23, 40 – 42].

Based on the above delineation of the underlying theoretical concepts, our working hypothesis is that our instrument demonstrates ample discriminatory power between two groups of participants: care-professionals and professionals from hospital management. This hypothesis is built according to social cognition theory proposing that socialization in various working contexts shapes people's cognitive schema (e.g. [11]). It is well-known from previous research that schemas strongly influence information processing, making people more likely to attend to, encode and recall information which match with the existing schemas (e.g., [36, 43]). In line with this, and because of being embedded in a working environment that expects from its members an orientation towards the principles of biomedical ethics which are also part of nurses' training programs in ethics, we hypothesized nurses to be more likely to demonstrate greater sensitivity for principle-related issues. Of note is the fact that although the principles form a separate cluster, this cluster has a much stronger affinity to the moral as opposed to the strategic cluster. In contrast, we hypothesized that members of hospital management demonstrate greater sensitivity for strategy-related issues. This is because they are more often faced with strategy- and business-related problems in their working life. We were indifferent about the expectations related to the other, more general moral values. Since both groups may be faced with problems tapping into issues of e.g. honesty or fairness, both may have evolved some sensitivity for such issues. Of main interest is, whether our measure is capable of revealing the expected group differences, supporting the validity of our instrument.

In conducting the group comparison, we recruited professionals from nursing on the one hand and from hospital management, administration and human resources on the other. As outlined, we aimed at demonstrating the instrument's capability to differentiate between these two cohorts (professionals from management: increased sensitivity for strategy-related issues, nursing professionals: increased sensitivity for values relevant in clinical practice, i.e. principle-related values).

3.2. Participants and Procedures

In this study, 57 participants from various clinics located in the German part of Switzerland filled out the questionnaire. After rigorous examination of the data, 48 datasets fulfilled our quality criteria: participants were required to self-categorize them to one of the two groups and were required to have patient contact either on a daily basis (nursing professionals) or fewer than once a month (hospital management). 37 (30 females) were nursing professionals whereas 11 (7 males) worked in the field of hospital management, human resources or administration. There was a statistically significant gender misbalance and mean age difference (mean age: nursing: 39 years, management: 48 years). This gender misbalance, however, is not surprising given that nursing and management are among the most sharply sex-segregated of occupations. The two groups did not significantly differ in the time needed for completing the questionnaire (see Table 2).

TABLE 2 ABOUT HERE PLEASE

In the questionnaire, we first assessed demographic information (gender, age, field of work) and information about participant's work experience in medicine (duration and frequency of contact to patients). Participants then were briefly instructed how to fill out the questionnaire. Subsequently, they were asked to put themselves into the role of a clinical expert in charge who is partly involved as a committee member of a clinical expert-group. They were told that currently, there were five cases (i.e. vignettes) to be discussed during the upcoming committee meeting during which they were expected to bring in spontaneously the considerations they deem important for the case evaluation. We explicitly noted that decisions about which concrete actions to take would be elaborated at a later time.

Next, the five vignettes were randomly presented on the computer screen: after having read one vignette which disappeared upon clicking the "next"-button, participants were provided with a list of 11 value-related statements (see Section 2.2. Step 2: value representation). Thus, participants were provided with all 11 values from the three clusters (i.e. in form of 11 statements) for the value selection step following vignette inspection. For most values, there were multiple statements which satisfied quality criteria (see step 2: value representation). Hence, we presented participants with the most suitable statements to content. They were asked to select those statements which they consider to be associated with the situation. They could select as many statements as they liked. This task was designed to examine which values participants recognize in each vignette. The vignette reappeared together with all previously chosen statements, and participants were asked to distribute points (i.e. allocate importance) to these statements. In total, 10 points had to be distributed to the statements, including the possibility that some statements could receive 0 points. This task was designed to assess the perceived importance of the selected value (see infographic for instrument process illustration purposes).

INFOGRAPHIC ABOUT HERE PLEASE

This procedure negates the possibility of “wrong” answers. Hence, we deliberately abstained from taking a normative stance of what is right and wrong. Morally sensitive individuals are generally more likely to associate moral values within ambiguous situations because they are expected to have more easily accessible moral schemas. As a result, they are also expected to be more likely to direct attention more or less automatically and swiftly to moral issues (see Section 3.1). This aligns with previous conceptualizations (e.g. see [42]) after which and as opposed to other ethics constructs (e.g. formalism) which hold a clear position on what is right and wrong, moral sensitivity has additional explanatory value in simply acknowledging that individuals are considering concepts associated with morality. Additionally, categorizing a perceived value as wrong in itself is a moral claim which would need justification in such a way that it would introduce the challenge of defining a deciding authority (i.e. who decides about the wrongness of a given value). In our view, the process of perception of values is a hermeneutical rather than absolutist process. Hence it would take a fairly strong and in fact paternalistic stance condemning certain perceptions as being plain wrong. Typically, the problem is perceiving not enough - and hence missing the important issues in a given situation rather than perceiving “wrong” issues.

Overall, we posit that flexible and pluralistic value-perception is superior to rigid and singular value perception even if this complicates moral decision-making and behavior at a later stage. Specifically, we hypothesize that multiple value perception reduces the risk of moral blindness [44] and hence unethical behavior. Multiplicity in value recognition, however, should not be understood as a form of relativism. Our notion refers to other claims [44] that good decisions depend on perspective-taking and imagination and thus the ability of an individual to appraise multiple aspects during decision making. It also supports tolerance rather than fundamentalism. The development of value sensitivity would face dramatic barriers if assessed in a context of strict and rigid right/wrong-definitions. Accordingly, it will only thrive in a permissive and open environment.

3.3. Calculating Value Sensitivity

Participant's value sensitivity scores were calculated by combining both a) the number of values recognized in each vignette and b) the importance attributed to these recognized values operationalized as the number of points assigned to those selected values. In this respect, value sensitivity is congruent with previous definitions of moral sensitivity as containing both the recognition and the ascription of importance of moral-related issues (see [6, 11, 42]). In order to calculate participant's value sensitivity for the three clusters, the mean number of recognized values for each cluster separately of the aggregated data of all five vignettes was calculated. Next, we calculated the total number of allocated points for each cluster and divided it by the total number of possible points. The mean of recognized values for each cluster was then multiplied with the normalized number of points allocated to the corresponding value-cluster.[1] Hence, we summed all recognized principle-related values across all vignettes and calculated the mean which was multiplied by the normalized value of points allocated to principle-related values for all vignettes in order to calculate the sensitivity for principle-related values. We calculated the sensitivity for the other two value clusters in the same way. Consequently, potential differences in perception between vignettes carried less weight.

3.3.1. Generalized definition of value-sensitivity computation:

Formally, the computation of value sensitivity is as follows: Let VS^M, VS^P, and VS^S denote the value sensitivity for moral-related values (M), principle-related values (P) or strategy-related values (S). Furtermore, let N^V be the number of vignettes used; K be the number of points that can be distributed to all chosen values per vignette; and N^M, N^P and N^S be the number of values per value group (M, P or S). Finally, let n_i^M, n_i^P and n_i^S be the number of values chosen per vignette i and group; and k_i^M, k_i^M, and k_i^M be the number of points attributed to moral-related, principle-related

[1] To exemplify calculation: If a person has (over all 5 vignettes) in the mean recognized 2 out of 4 values of the moral cluster, the "recognition rate" would be 0.5. And if this person has (again over all 5 vignettes) attributed in total 10 out of 50 possible points (i.e., 10 possible points times 5 vignettes) to those values, the normalized number of points would be 0.2. Hence, the result related to the moral values for this person would be 0.5*0.2 = 0.1.

and strategy-related values per vignette i. Then the generalized definition of value sensitivity is given as:

$$VS^{M,P,S} = \frac{1}{N^V\ N^{M,P,S}} \sum_{i=1}^{N^V} n_i^{M,P,S} \times \frac{1}{N^V\ K} \sum_{i=1}^{N^V} k_i^{M,P,S}$$

In our case, $N^V = 5$, $K = 10$ and (for example) $N^M = 4$. Thus, the sensitivity for moral values is calculated as:

$$VS^M = \frac{1}{20} \sum_{i=1}^{5} n_i^M \times \frac{1}{50} \sum_{i=1}^{5} k_i^M$$

The calculation of VS^P and VS^S is analogous ($N^P = 4$, $N^S = 3$).

3.4. Results of validation study

A Shapiro-Wilk-test analyzing normality was performed and highlighted non-normality for sensibility for strategy-related values. We therefore conducted a Mann-Whitney U Test as a non-parametric test. Statistical significance was accepted at a $p \leq 0.05$ level.

We compared value sensitivity of nurses and hospital managers for the three value groups (moral-related values, principle-related values, strategy-related values) (see Fig 1). In terms of sensitivity for principle-related values (see Fig 1a), the group comparison yielded a significant difference with nurses (*M = 0.39, SD = 0.12*) revealing higher scores than management professionals (*M = 0.32, SD = 0.09*) (*U (125.00) = -1.93, p = 0.05*). In terms of sensitivity for strategy-related values (see Fig 1b), we found another significant difference between the groups, with professionals from hospital management revealing higher scores (*M = 0.11, SD = 0.08*) than nurses (*M = 0.05, SD = 0.07*) (*U*

(110.00) = -2.30, p = 0.02). In terms of sensitivity for moral-related values, we found no significant differences between the groups ($p > 0.35$) (Fig 1c). Consequently, our instrument was able to discriminate between nursing- and management professionals as our hypothesis predicted.

Next, we tested for potential gender differences. A Mann-Whitney U test yielded the following results: males ($M = 0.11, SD = 0.09$) demonstrated a significantly greater sensitivity for strategy-related values compared to females ($M = 0.04, SD = 0.06$) ($U (122.50) = -2.63, p = 0.01$). On the other hand, females ($M = 0.39, SD = 0.12$) demonstrated a greater sensitivity for principle-related values compared to males ($M = 0.33, SD = 0.10$) ($U (152.50) = -1.94, p = 0.05$). There was no significant gender difference regarding sensitivity for moral-related values ($p > 0.65$).

Finally, the analysis of the frequency of each value selected by participants across vignettes demonstrated only minimal differences (6 comparisons of 110 involving 3 values (cost-efficiency, autonomy, loyalty – one of every cluster) yielded a significant result only). This may corroborate our negation of “wrong” value attribution (see Supplementary Materials for a table indicating the choices and what was selected by each group (Table 3)).

FIG 1 ABOUT HERE PLEASE

4. Discussion & Conclusion

4.1. Group Comparison & Limitations

In the context of this research project, we were successful in executing a first trial of validity testing of our developed tool for the measure of context specific value-sensitivity. Significant differences emerged when comparing professionals from nursing compared with experts from hospital management and -administration. More specifically, nursing professionals demonstrated greater sensitivity for principle-related values, while professionals from hospital management and administration revealed greater sensitivity for strategy-related values. This confirms our hypothesis. Finally, groups did not significantly differ on other, more general moral-related values. As outlined previously, we think that both groups may be faced with problems tapping into issues such as honesty and fairness, which might explain the indifference of the two groups.

This study incorporates the following limitations. First, we are well aware of the fact that group comparisons are only one step of validating instruments. Future studies are needed to further test the instrument. In line with this, we are currently running studies aiming at assessing concurrent as well as convergent validity by comparing our instrument with other congruent or non-congruent questionnaires. Furthermore, we are in the process of complementing the instrument with an implicit measure. Hence, more research is needed for the development of an instrument that is able to assess value sensitivity at an individual level.

Second, due to the small sample size, hospital managers and administrators used in this study might not be representatives of their profession. Moreover, the generally low level of strategic sensitivity for both groups might have been extrinsically induced by application of an unbalanced stimulus material: both, the moral- and principle-related value clusters are composed of 4 values each, whereas the strategy-related value cluster only consisted of 3 values. Hence, the pure likelihood to choose a strategic value was smaller.

Third, one has to take into account that, based on the small sample size of at least one group and because of a non-randomized study design, there might be intrinsic differences between the individuals of the two groups related to gender. Furthermore, we are unable to fully explore the effects of gender detached from the domain of occupation, since gender was endogenous to domain of occupation. The influence of gender on morality is controversially discussed and appears also to depend on age, level of education, occupation and their interrelation [45]. Whilst studies investigating gender differences are largely controversial, in most cases when gender differences can be identified, women tend to show greater levels of moral awareness, particularly when studies focus more closely on care-based moral convictions [29, 46].

Finally, another important point is that the increased sensitivity for strategy-related values of managers and the decreased sensitivity for principle-related values should not be interpreted to suggest that managers are "less moral" compared to nurses. We emphasize that our conceptualization of value sensitivity favors the notion that an increased strategic sensitivity is not per se ethically less desirable. Rather, professionals of a specific occupation are expected to demonstrate a sensitivity that aligns directly with their occupation-related values. Such a sensitivity is important because a manager who is not aware of concepts including e.g. cost-effectiveness, will not succeed in his daily work. Furthermore, an insensitivity in this respect may very well induce negative consequences for employees in the institution and therefore does have ethical implications. Apart from that, managers did not differ in their sensitivity related to other, more general moral values. It would therefore be desirable to have design interventions at one's disposal for improving professionals' sensitivity without compromising their occupation-related thinking. In the end, such sensitivities should not substitute but supplement each other.

4.2. Ethical questions related to a potential deployment of an instrument of this sort

4.2.1. Potential benefits of improving MS

Patients and their family members are increasingly demanding empowerment and the desire to be involved in clinical decisions. Medical decision-making authority is being questioned, self-determination of patients is gaining importance and the patient is increasingly perceived as a partner in a shared decision making process [47]. Consequently, appropriate clinical and moral decision-making is not performed in a paternalistic way, but increasingly demands certain kinds of sensitivities in pluralistic societies. As outlined previously, in such situations, healthcare providers need to recognize and appraise morally relevant issues immediately which requires both appropriate cognitive and balanced emotional processes (see Section 1). Moral sensitivity ideally would render agents sensitive to peculiar issues and support them in classifying their immediate perceptions. Supporting health care providers in coping with dilemmatic situations and vulnerable patients represents a primary relevant ethical duty because caring holistically for patients not only represents a duty-based quality but also benefits patients, healthcare providers and the clinic as a whole. Moral sensitivity may support the quality of caring by helping people to be better attuned to patients' needs and demands. In general, agents with greater moral competences may reduce costs by acting swifter and in a more confident way. As such, being sensitive in the desired way and within a "healthy" range (see next paragraph) is certainly likely to be a desirable quality as it could improve clinical support and may diminish psychological stress (e.g. feelings of uncertainty) of healthcare professionals. Simultaneously, patients could benefit from more individualized and sensitive care. Moreover, incorporating values, opinions and fears of different stakeholders such as representative family members might prevent long-term psychosocial problems.

In addition, organizational structures may inhibit abilities of health care providers to be sensitive to the moral content of everyday practice and may also evoke stress-related disorders of which many health care professionals suffer (be it by institutional constraints, or when professionals clash with legal regulations when following moral decisions) [48]. Furthermore, lack of time, skills and interpersonal support have been directly associated with decreased moral sensitivity [49]. If professionals are more clear and confident about which strategy to pursue due to greater moral sensitivity (e.g. following sensitivity-training), they are more likely to overcome constraints more easily.

4.2.2. Risks of improving moral sensitivity

While the ability of being morally sensitive to moral issues is likely to have a number of positive consequences, moral sensitivity might also have negative consequences. An individual sensitive to moral issues might be unable to act and might suffer from the psychological burden a given situation holds. Being morally sensitive is not per se a desirable quality. It can be maladaptive for the individual and society. Hence, it is not clear whether enhancing moral sensitivity should be considered desirable in all circumstances. Healthcare providers who demonstrate a marked sensitivity might be unable to comply with the economic and structural regulations that predominate within a clinic. They also might suffer from emotional overload or increased moral distress (i.e. the felt incompatibility to reconcile own moral decisions and stiff legal regulations). Furthermore, healthcare providers with high moral sensitivity may be subjected to more dilemmatic situations, which may hinder appropriate clinical acting. Alternatively, individuals who exercise marked sensitivity might be evaluated as behaving inappropriately due to exaggerated levels of empathy associated with being unable to discern privacy signals. The latter phenomenon has already been described as exaggerated and inappropriate approach-behaviors (i.e. hypersocial drive) in the case of disorders of hypersociability like Williams Syndrome [50]. It also might be problematic if nurses are completely honest with patients in all contexts. This is consistent with Weaver's [10] recent criticism of bias in the literature in uncritically accepting moral sensitivity as having only positive consequences, while neglecting potential negative implications. With regard to care services, Weaver also suggested that negative states, such as emotional overload, exploitation or moral distress could result from a higher level of moral sensitivity. Similarly, Morioka [51] posited that a society with a plenty of morally sensitive people might be considered a good society, but people living in such a society might not necessarily be happy, because they worry about every immoral and unfair deed. While it is per se ethical to be morally sensitive, it might very well be strategically unfavourable and ultimately bad for the individual if one is morally sensitive in a culture which negates moral sensitivity. There is need for a concise evaluation of whether and under which circumstances increased moral sensitivity might be beneficial at an individual compared to a societal level. Because individual values are formed through socialization in a context of normative beliefs, a discussion involving a distinction between the individual and society may also need a discussion on the relation of individual values as a reflection of social categories.

4.2.3. Potentials and limits of instruments

Potential fields of application include the deployment of such an instrument in the context of primary and continued education besides the staff-selection domain. After us, the first field of application appears to be more suitable whereas the latter involves a greater degree of ethical risk. As outlined previously, knowledge about one's strengths and weaknesses combined with the possibility for their specific modulation would clearly be advantageous. Using such an instrument for personnel procurement purposes however, is more critical. In this context, it is important to emphasize that results from such instruments are generally vulnerable to error. Hence, the methodological step of validation is important in order to minimize the risk of misjudgment. In addition, it is difficult to make long-term prognoses in the context of psychological assessments mainly because a multitude of factors might exert modulatory influences. Instruments are typically being used in combination with other assessment strategies. Finally, it should be openly discussed to whom the generated data of the assessment belong, how and whether the data should be stored and anonymized in order to prevent misuse and whether such data should be made available for other organizations and companies (e.g. as quality assessments for teachers or medical students before entering medical school). To answer those questions, it will be vital to perform an in-depth analysis specifically addressing under which criteria and in which context privacy might overrule and prevent assessment-performers from disclosing data. If used as an assessment instrument for entering specific occupational trainings, pressure for interested individuals might increase. Other consequences of such assessments are privacy concerns and the danger of stigmatizing individuals.

5. Outlook & Conclusions

Living a moral life is not simply a matter of following a set of learned moral rules and of learning how to apply these rules to specific situations. By emphasizing the psychological basis relevant for moral behavior, one (1) acknowledges the increased scientific understanding of the foundations of moral behavior and (2) thereby has the possibility to carve out and provide means for their specific modulation. In this research project, we attempted to incorporate current knowledge from social and moral psychology in order to develop an instrument that allows for a status-quo assessment of ones' value sensitivity in the clinical care context that anticipates an additive possibility of specifically training the underlying competency. This idea aligns with virtue ethics by paying attention to our habits of character and developing these in order to act in a moral way.

We believe that the proposed instrument provides the following advantages: (1) previous research suggests that value-sensitivity is domain specific (see [4]). Identifying specific subcomponents of value-sensitivity for different domains (e.g. values that are especially relevant for a specific domain solely) or semantically varying values (e.g. transparency in the economic field, honesty in medicine) becomes a crucial task for developing instruments aimed at assessing and increasing value-sensitivity. (2) The instrument is thought to represent a flexibly adaptable basic module if understood as a loosely tool of interchangeable building blocks. This involves relevant values for the specific context that can be identified and enacted. The instrument can then be complemented by incorporating more – or simplified by incorporating less – values by adhering to our procedure. (3) The instrument provides a fully automated data acquisition process and could easily be extended by an automated analysis algorithm providing users with an instant status-quo assessment of ones' moral profile. Therefore, the time consuming steps of post-coding open answers are omitted. Finally,

(4) we intend to complement the instrument by an implicit measure in order to further accommodate insights gained from psychological research.

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Competing interests

The authors declare that they have no competing interest.

Authors' contributions

MC and CT designed the study, CI and MC executed the study, CI and MC performed the data analysis. All authors were involved in preparing the manuscript.

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Figures legends

Figure 1: Group comparisons for moral-related, principle-related and strategy-related value sensitivity.

Tables including titles

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Table 1: Mean value quality analysis of vignettes

	Quality-criteria						moral ambiguity					
	Comprehensibility		Expert knowledge		Relation to reality		strategic		moral		Δ	
Vignette No	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	(SD)	p
1	1.63	(0.89)	1.69	(0.80)	1.62	(0.62)	4.19	(0.98)	4.19	(0.75)	(1.42)	1.000
2	1.76	(0.83)	1.94	(1.03)	2.12	(0.86)	4.65	(0.79)	3.41	(1.00)	(1.25)	0.001**
3	1.63	(0.89)	2.81	(1.11)	1.38	(0.62)	3.38	(1.54)	3.88	(0.89)	(1.86)	0.300
4	1.82	(0.81)	2.59	(1.00)	2.18	(0.88)	4.59	(0.62)	3.82	(1.02)	(1.26)	0.023*
5	1.41	(0.87)	1.59	(1.00)	2.24	(0.75)	4.18	(0.95)	4.29	(0.85)	(0.78)	0.543
6	2.5	(1.32)	2.63	(1.31)	1.69	(0.70)	3.53	(1.06)	3.53	(0.83)	(1.46)	1.000
7	1.89	(0.94)	3.16	(1.07)	1.79	(0.86)	4.21	(1.03)	4.26	(0.93)	(1.13)	0.841

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8	1.35	(0.59)	2.35	(1.23)	1.75	(0.91)	4.1	(0.97)	4.95	(0.22)		(0.99)	0.001**
9	1.84	(1.17)	3.26	(1.05)	2.47	(1.17)	2.53	(1.07)	4.21	(0.98)		(1.29)	0.000***
10	1.52	(0.81)	2.62	(1.12)	1.29	(0.56)	3.81	(1.03)	4.9	(0.30)		(1.04)	0.000***
11	1.83	(0.86)	2.33	(1.24)	2.5	(0.86)	4.61	(1.15)	3.56	(1.34)		(1.83)	0.026*
12	1.62	(0.5)	2.75	(0.93)	1.75	(0.68)	3.44	(1.41)	4.75	(0.78)		(1.49)	0.003**

remark : vignettes (**bold**) were selected if: $M_{comprehensibility} \leq 2.5$, $1.5 < M_{expert\_knowledge} < 3.5$, $M_{relation\_to\_reality} < 2.5$, $M_{moral/strategic} < 4.5$, Δns; * $p < .05$, ** $p < .01$, *** $p < .001$

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Table 2: demographic differences of groups

	Nursing	Management	Significance level
Number of participants	37	11	
Mean age [years]	39	48	MW: p=0.01
Years of employment	17	15	n.s.
Gender-ratio	f: 30, m: 7	f: 4, m: 7	MW: p=0.005
Time needed for filling out questionnaire [min]	39	44	n.s.

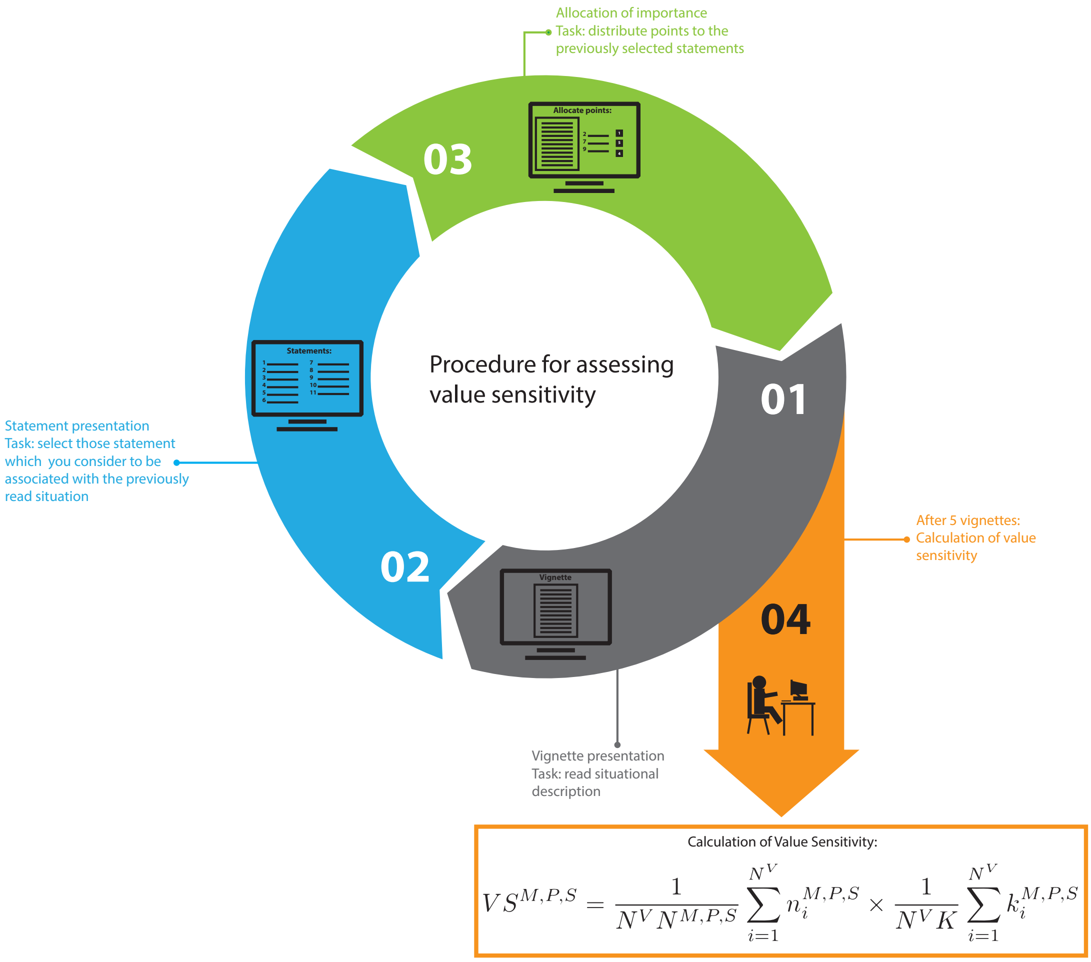
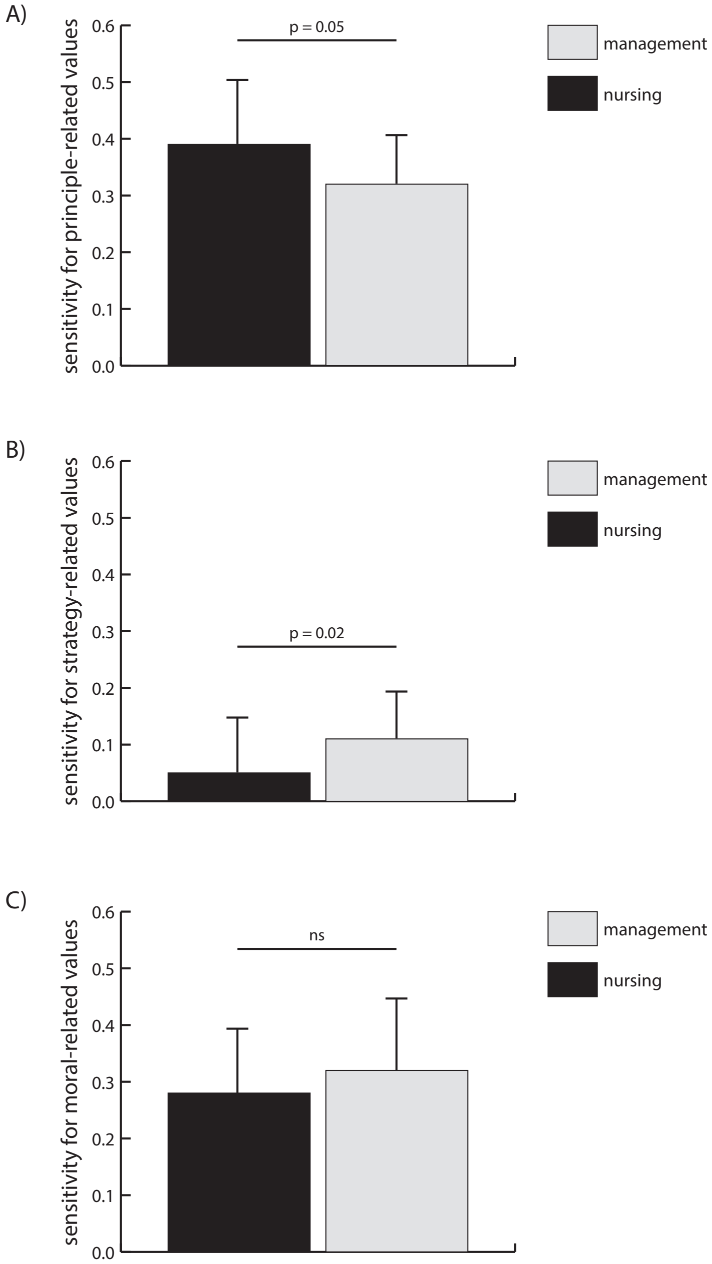

Allocation of importance
Task: distribute points to the previously selected statements
Allocate points:
03
Statements:
Statement presentation
Task: select those statement which you consider to be associated with the previously read situation
02
Procedure for assessing value sensitivity
01
Vignette
Vignette presentation
Task: read situational description
04
After 5 vignettes: Calculation of value sensitivity
Calculation of Value Sensitivity:
$$VS^{M,P,S} = \frac{1}{N^V N^{M,P,S}} \sum_{i=1}^{N^V} n_i^{M,P,S} \times \frac{1}{N^V K} \sum_{i=1}^{N^V} k_i^{M,P,S}$$

Fig 1)


A)
p = 0.05
sensitivity for principle-related values
0.6
0.5
0.4
0.3
0.2
0.1
0.0
management
nursing
B)
p = 0.02
sensitivity for strategy-related values
0.6
0.5
0.4
0.3
0.2
0.1
0.0
management
nursing
C)
ns
sensitivity for moral-related values
0.6
0.5
0.4
0.3
0.2
0.1
0.0
management
nursing

Supplementary Materials:

Table 1a (Statements in German)

Representativeness of statements

Value	Statement	M	(SD)
Fürsorge	*Wenn eine Therapie machbar ist, soll sie auch umgesetzt werden*	*4.04*	*(1.45)*
(n = 282)	Ein Arzt oder eine Pflegekraft soll Menschen, die sich selbst nicht helfen können, Beistand leisten.	5.37	(0.88)
	Man soll sich aktiv für die Förderung von Gesundheit und Wohlbefinden von Patienten einsetzen.	5.36	(0.94)
	Ein Patient soll sich in einer Institution geborgen fühlen.	5.00	(1.09)
	Patienten sind darin zu unterstützen, wieder selbst ein gutes Leben führen zu können.	5.18	(0.97)
Leistung	Für persönliche Verdienste sollte man auch persönlich belohnt werden.	4.63	(1.21)
(n = 276)	*Auch in Abwesenheit von Regeln sollte auf einen korrekten Umgang geachtet werden.*	*4.38*	*(1.68)*
	Mitarbeiter sollen Überstunden leisten, wenn die Umstände dies erfordern.	4.29	(1.27)
	Personen sollten alles daran setzen, die gesteckten Ziele zu erreichen.	4.92	(1.13)
	Vorgesetzte sollten stets das Maximum aus ihrem Team herausholen.	4.78	(1.15)
Wirtschaftlichkeit	Institutionen im Gesundheitswesen müssen kostenbewusst arbeiten.	4.71	(1.31)
(n = 284)	Die Kosten einer Therapie dürfen beim Entscheid für oder wider ihres Einsatzes eine Rolle spielen.	4.14	(1.61)

	Ärzte sollen Aufwand und Nutzen einer medizinischen Intervention abwägen.	4.66	(1.41)
	Medizinische Mittel sollten möglichst sparsam eingesetzt werden.	3.82	(1.55)
	Die Patienten sollten einen stets korrekten Umgang erwarten können.	*3.6*	*(1.96)*
Reputation	Medizinische Institutionen sollten ihr öffentliches Image pflegen.	4.69	(1.17)
(n = 286)	Handlungen sollten dahingehend überprüft werden, wie sie von anderen beurteilt werden.	4.09	(1.50)
	Ein Arzt sollte auf seinem Gebiet eine anerkannte Kapazität sein.	4.73	(1.12)
	Eine Person ist ein zuverlässiges Mitglied seiner Gemeinschaft.	*4.02*	*(1.47)*
	Mitarbeiter sollten sich so verhalten, dass sie positiv beurteilt werden.	4.42	(1.35)
Autonomie	Ein Patient soll über eine Therapie frei von Einflüssen von aussen entscheiden.	4.95	(1.21)
(n = 282)	*Ein Arzt sollte versuchen die Ergebnisse seiner Arbeit stets zu verbessern.*	*3.85*	*(1.72)*
	Es ist anzustreben, dass Patienten ein möglichst eigenständiges Leben führen können.	5.29	(0.87)
	Auch wenn es einer Person schadet, darf diese eine medizinische Behandlung ablehnen.	5.45	(0.89)
	Der Arzt soll nicht versuchen, eigene Therapiepräferenzen dem Patienten aufzudrängen.	4.94	(1.26)
Respekt	Die Privatsphäre und Selbstbestimmung einer Person ist zu achten.	5.51	(0.74)
(n = 280)	Es sollte ein wertschätzender Umgang mit den Patienten gepflegt werden.	5.59	(0.71)
	Man sollte die Würde von Patienten achten.	5.63	(0.72)
	Patienten wie Mitarbeiter sollten hochachtungsvoll behandelt werden.	5.44	(0.79)

	Riskante Therapien sollten vermieden werden.	*2.99*	*(1.42)*
Nicht-Schaden	Andere sind vor Leid und negativen Auswirkungen zu bewahren.	5.14	(1.01)
(n = 283)	Es ist darauf zu achten, dass anderen durch eigenes Handeln nicht geschadet wird.	5.27	(1.06)
	Jegliche medizinische Intervention muss mehr Nutzen als Schaden stiften.	5.03	(1.21)
	Auch medizinische Institutionen sollten auf Rentabilität achten.	*2.92*	*(1.49)*
	Patienten sollten keinen vermeidbaren Risiken ausgesetzt werden.	5.24	(1.01)
Loyalität	Eine Person sollte zum Team und zu einer gemeinsamen Sache stehen.	5.21	(0.90)
(n = 283)	Eine Institution sollte sich auf die Treue seiner Mitarbeiter verlassen können.	4.97	(1.01)
	Auch bei schwierigen Entscheidungen unterstützt man die Entscheidung der Verantwortungsträger.	4.71	(1.07)
	Langjähriger Einsatz für eine gemeinsame Sache sollte honoriert werden.	4.82	(1.01)
	Andere sollten als selbstbestimmte und einzigartige Individuen akzeptiert werden.	*4.05*	*(1.56)*
Ehrlichkeit	Die Kommunikation mit Patienten soll aufrichtig und offen sein.	5.69	(0.61)
(n = 281)	Die Leitung einer Institution sollte seine Mitarbeiter transparent über anstehende Veränderungen informieren.	5.42	(0.83)
	Patienten und Angehörige sollten mit allen relevanten Informationen versorgt werden.	5.56	(0.78)
	Sind in einer Institution Probleme entstanden, darf die Öffentlichkeit nicht fehlinformiert werden.	5.22	(0.97)
	Eine Person soll den ihr zugewiesenen Handlungsspielraum im Griff haben.	*4.08*	*(1.61)*

Gerechtigkeit	Niemand sollte ungerechtfertigt bevorzugt werden.	5.64	(0.75)
(n = 291)	Man sollte sich anderen gegenüber so verhalten, wie man es sich auch von diesen wünschen würde.	5.17	(1.13)
	Gemeinsam definierte Regeln sind einzuhalten.	4.98	(1.13)
	Wichtige Entscheidungen sollten unvoreingenommen getroffen werden.	5.04	(1.13)
	Ein gutes Ansehen bei Patienten sollte mit allen Mitteln gewahrt werden.	*2.89*	*(1.54)*
Verantwortung	Man soll eigenständig handeln und über seine Handlungen Rechenschaft ablegen.	4.98	(1.08)
(n = 286)	Schäden, die durch die eigenen Handlungen entstehen, sollen von einem selbst übernommen werden.	4.60	(1.37)
	Die unterschiedlichen Ansprüche relevanter Gruppen sollten angemessen berücksichtigt werden.	4.19	(1.37)
	Eine medizinische Institution sollte seine Pflichten gegenüber der Gesellschaft wahrnehmen.	5.20	(0.93)
	Ein Arzt oder eine Pflegekraft soll sich um das Wohlergehen eines Patienten sorgen.	*5.16*	*(1.12)*

Remark : Distractors are indicated in *italics*.

ENGLISH TRANSLATION (translation has not been reviewed (i.e. no back-translation has been performed)):

Table 1b (statements in English)

Representativeness of statements

Value	Statement	M	(SD)
Care	*If a therapy can be realized, it should be executed.*	*4.04*	*(1.45)*
(n = 282)	A physician or a caregiver should provide assistance to patients who cannot help themselves.	5.37	(0.88)
	One should promote health and well-being of patients in a thorough way.	5.36	(0.94)
	A patient should feel save in a given institution.	5.00	(1.09)
	Patients should be supported in regaining an autonomous life.	5.18	(0.97)
Performance	Personal merits should be rewarded individually.	4.63	(1.21)
(n = 276)	*Also in the absence of explicit rules, a correct social interaction should be respected.*	*4.38*	*(1.68)*
	Coworkers should execute hours of overtime, if the circumstances require it.	4.29	(1.27)
	Individuals should do everything possible to accomplish aspired goals.	4.92	(1.13)
	Chefs should always push members of their team to the maximum/limits.	4.78	(1.15)
Cost-effectiveness	Institutions in the health care system have to work under the consideration of cost-efficiency.	4.71	(1.31)
(n = 284)	The costs of a given therapy should be of importance when evaluating decisions involving therapeutic strategies.	4.14	(1.61)
	Physicians should weigh costs and benefit for a given medical intervention.	4.66	(1.41)

	Medical goods should be used as sparingly as possible.	3.82	(1.55)
	Die Patienten sollten einen stets korrekten Umgang erwarten können.	*3.6*	*(1.96)*
Reputation	Institutions should care about their public image.	4.69	(1.17)
(n = 286)	Actions should be reviewed with regard to how others would judge those.	4.09	(1.50)
	A physician should be a known capacity in his field.	4.73	(1.12)
	A person should be a reliable member of the society.	*4.02*	*(1.47)*
	Coworkers should perform in order to be evaluated positively.	4.42	(1.35)
Autonomy	A patient should be able to give consent for a therapeutic intervention without any influences from outside.	4.95	(1.21)
(n = 282)	*A physician should try to constantly improve the results of his work.*	*3.85*	*(1.72)*
	It should be aspired that patients can live an independent life.	5.29	(0.87)
	Even if it harms an individual, he/she has the right to refuse a medical treatment.	5.45	(0.89)
	A physician should not try to force his or her medical preference on a patient.	4.94	(1.26)
Respect	The privacy and self-determination capacity of persons should be respected.	5.51	(0.74)
(n = 280)	A cherished contact with the patients should be cultivated.	5.59	(0.71)
	One should respect the human dignity of patients.	5.63	(0.72)
	Patients and coworkers should be treated respectfully.	5.44	(0.79)
	Risky therapies should be avoided.	*2.99*	*(1.42)*

Nonmaleficence	One should pay attention not to harm others.	5.14	(1.01)
(n = 283)	Others should be prevented from suffering and distress.	5.27	(1.06)
	Any medical intervention should endow more benefit than harm.	5.03	(1.21)
	Medical institutions should pay attention to aspects of profitability as well.	*2.92*	*(1.49)*
	Patients should not be exposed to avoidable risks.	5.24	(1.01)
Loyalty	A person should adhere to his team or a shared cause.	5.21	(0.90)
(n = 283)	An institution should be able to rely on its coworkers.	4.97	(1.01)
	Also in times of troubles, one supports the decisions of the people in charge.	4.71	(1.07)
	Long-term dedication/commitment for a shared cause should be rewarded.	4.82	(1.01)
	Others should be recognized as autonomous and individual / unique persons.	*4.05*	*(1.56)*
Honesty	The communication with patients or customers should be sincere and frankly.	5.69	(0.61)
(n = 281)	The leadership of an institution should inform its coworkers transparently about upcoming changes.	5.42	(0.83)
	Patients and affiliated persons should be provided with all relevant information.	5.56	(0.78)
	If there have emerged institutional problems, the public should not be misinformed.	5.22	(0.97)
	A person should master his/her assigned scope of action.	*4.08*	*(1.61)*
Justice	Nobody should be favored in an unjustified way.	5.64	(0.75)
(n = 291)	One should act according to how one would desire to be treated him/herself.	5.17	(1.13)

	Mutually defined rules should be maintained.	4.98	(1.13)
	Important decisions should be made unprejudiced.	5.04	(1.13)
	A solid reputation should be protected by all means.	*2.89*	*(1.54)*
Responsibility	One should act independently and be accountable for his actions. .	4.98	(1.08)
(n = 286)	Damage which is due to one's actions should be adopted by oneself.	4.60	(1.37)
	The diverse interests of relevant groups should be regarded appropriately.	4.19	(1.37)
	An institution should recognize its obligations towards society.	5.20	(0.93)
	A physician or a caregiver should care for the wellbeing of a patient.	*5.16*	*(1.12)*

Remark : Distractors are indicated in *italics*.

Table 2: distractor analysis

Paired sample t-test of mean value statements compared to distractors.

Value group	M_stat	M_dist	p-value
care	5.00	4.04	p = 0.000
reputation	4.09	4.02	p = 0.606
non-maleficence	5.03	2.92	p = 0.000
honesty	5.22	4.08	p = 0.000
performance*	4.63	4.38	p = 0.038
cost-effectiveness	3.82	3.60	p = 0.172
autonomy	4.94	3.85	p = 0.000
respect	5.44	2.99	p = 0.000
loyalty	4.71	4.05	p = 0.000
justice	4.98	2.89	p = 0.000
responsibility†	x	x	x

Remark: lowest mean values of value-statements (M_stat) were compared to the mean values of the distractors (M_dist) localized in the same value group. * indicates that the 2nd lowest M_stat was taken because the lowest value statement was below M_dist (see main text for explanations). For †, no comparison was performed because M_dist yielded the second highest value.

Table 3: Choices and selections by group (nurses vs professionals from management and administration) for every vignette (V1-V5) and all 11 values (first column) with respect to the aggregated number of value-selections (values) and the attributed number of points (points) to these same values.

	V1				V2				V3				V4				V5			
	Nurses		Managers		Nurses		Managers		Nurses		Managers		Nurses		Managers		Nurses		Managers	
	values	points	values	points	values	points	values	points	values	points	values	points	values	points	values	points	values	points	values	points
CAR	28	25	8	4	28	38	8	6	37	91	10	12	34	40	9	9	33	66	9	5
PER	16	22	6	4	10	5	4	6	12	4	6	1	4	4	4	0	10	1	3	1
CEF	14	10	7	9	16	17	6	8	23	18	10	11	27	33	9	13	29	33	10	15
REP	20	7	6	8	15	2	7	10	16	3	7	2	17	9	5	4	12	1	7	5
AUT	15	11	3	2	30	61	10	13	35	90	10	19	33	58	8	15	31	42	9	16
RES	33	69	10	30	26	43	7	9	34	72	11	28	34	65	10	24	32	55	11	18
NMA	27	47	8	15	32	64	10	16	22	20	8	10	35	60	9	18	32	64	11	21
LOY	28	20	6	8	13	6	2	4	9	2	8	3	12	1	7	2	13	5	7	2
HON	36	99	11	19	33	79	11	18	26	37	10	10	36	89	11	14	37	70	11	21
JUS	29	40	8	6	28	33	9	15	22	24	8	7	24	7	8	11	31	27	9	4
RPS	19	20	5	5	20	22	6	5	23	9	9	5	14	4	5	0	17	6	7	2

Selected vignettes (in German):

Vignette 1:

Dr. P, ein erfahrener Onkologe in der Klinik, hat in der Vergangenheit bereits mehrfach Angebote anderer Kliniken erhalten, diese aber aufgrund der Verwurzelung an die hiesige Klinik und seiner Wohnsituation wegen, immer abgelehnt. Doch seit letzter Zeit gibt es zwischen der Klinikdirektion und ihm als Leiter des onkologischen Zentrums Unstimmigkeiten bezüglich studentischer Ausbildungsmodalitäten, patientenorientierten Informationsbestimmungen und dem Einrichten einer Palliativstation, der Dr. P. kritisch gegenüber steht. Seit dem frühzeitigen Ableben seiner Frau ist Dr. P. gegenüber den Patientinnen und Patienten noch stärker engagiert, seine Skepsis gegenüber Neuerungen ist aber ebenfalls gewachsen, was zu Konflikten mit anderen leitenden Ärztinnen und Ärzten führt. Derzeit laufen Diskussionen zu diesen Punkten zwischen Klinikdirektion und den anderen leitenden Ärzten. Unter anderem wird erwogen, ob man sich wegen der gestörten Harmonie und in Konsequenz des fehlenden einheitlichen Lösungsbestrebens besser von Dr. P. trennen sollte. Wie soll die Klinikleitung diese Situation beurteilen?

Vignette 3:

Frau J., eine Patientin mittleren Alters, muss sich infolge einer Fussgelenksverletzung einer Operation unterziehen. Obgleich eine Routineoperation, wird diese infolge Versicherungsmodalitäten von der leitenden Oberärztin der Chirurgie durchgeführt. Am Tag nach der Operation erfolgt das Austrittsgespräch, bei dem die Oberärztin und ein Krankenpfleger anwesend sind. Die Oberärztin erklärt der Patientin die Wichtigkeit einer Thromboseprophylaxe, für die das Medikament Heparin subkutan mittels einer dünnen Kanüle injiziert werden muss, ähnlich wie bei der Insulin-Selbstgabe. Vier Tage nach der Entlassung wird die Patientin notfallmässig mit Atem- und Herzrhythmusstörungen eingeliefert. Sofort wird klar, dass eine Lungenembolie vorliegt. Der Notfallarzt vermutet eine unzureichende Thromboseprophylaxe. Nachfragen bei der Patientin ergeben, dass diese nicht genau wusste, wie sie bei der Heparin-Injektion vorgehen sollte. Ein danach anschliessendes Gespräch zwischen dem Notarzt und der leitenden Oberärztin der Chirurgie ergab keine Klärung der Sachlage, da üblicherweise der Krankenpfleger die Prophylaxe erklärt, im konkreten Fall aber die Oberärztin dies offenbar tat. Die Klinikleitung muss den Fall nun begutachten und das Vorgehen der Mitarbeiter beurteilen. Auf welche Aspekte soll diese dabei achten?

Vignette 5:

Im Pflegeheim der Institution ist seit einigen Wochen ein neuer Bewohner eingetroffen, ein exzentrischer Künstler, 65 Jahre alt, der seine Atelierwohnung aufgrund zunehmender dementieller Episoden verlassen musste. Bald wird klar, dass ein gewisses Bedürfnis, seine Kunst auszuleben zu können, weiterhin besteht. Dies wiederspiegelt sich in einem ständigen Verlangen, künstlerisch tätig zu sein. Der Mann stellt die Pflegenden mit diesem Wunsch sowie seiner stark ausgeprägten Individualität zwar immer wieder vor gewisse Herausforderungen, wird ansonsten von den Pflegenden als ein auf sich bezogener, einzelgängerischen, relativ ruhigen Heimbewohner beschrieben, der ein eher zurückgezogenes Heimleben zu führen scheint. Seit kurzem ist der Mann nun kaum mehr von seiner Idee abzubringen, im Hobbyraum des Pflegeheims ein kleines Atelier *einrichten zu wollen, wo er seinem Bedürfnis, künstlerisch wirken zu können, nachgehen könnte. Dieses Bestreben, welches einiger Umstrukturierungen bedürfte, wird von einigen Mitbewohnerinnen und -bewohner unterstützt; die Mitarbeiter allerdings haben mit Blick auf Personalplanung und längerfristige Konsequenzen Bedenken. Wie soll die Leitung des Pflegeheims diese Situation beurteilen?*

Vignette 6:

Prof. M. – ebenfalls Mitglied der Expertengruppe – ist eine anerkannte Forscherin im Bereich Migräne- und Schmerzforschung. Sie berichtet, sie habe kürzlich an einem Kongress von einer neuen klinischen Studie gehört, innerhalb welcher ein vielversprechender Wirkstoff getestet wird. In dieser Studie wurde auch ersichtlich, dass der Wirkstoff Verdauungsstörungen hervorrufen kann, die sich normalerweise mit einer längeren Einnahme verflüchtigen. Sie ist von den Studienerstellern direkt angesprochen und gefragt worden, ob Sie zusätzliche Patienten für die Studie rekrutieren könne. Nach der Rückkehr vom Kongress trifft sie in ihrer Sprechstunde auf Frau P., eine 45-jährige Patientin, sozial eingebunden, die seit ihrem 35. Altersjahr unter regelmässig wiederkehrenden Migräneanfällen leidet. Diese verunmöglichen es ihr zuweilen, ihren privaten wie auch beruflichen Verpflichtungen nachzukommen. Prof. M. informiert Frau P. routinemässig über das Studiendesign, worauf Frau P., von der Idee sehr angetan, sich einen Eintritt in die klinische Studie überlegt. Prof M. ist sich sicher, dass Sie aufgrund ihrer Kontakte Frau P. einen Platz in der Studie verschaffen könnte. Sie fragt die Expertengruppe, welche Informationspflichten Sie als „Schnittstelle“ zwischen Patientin und Studienteam habe. Auf was soll die Expertengruppe bei ihrer Antwort achten?

Vignette 7:

Für das zehnjährige ADHS-Kind Peter, bei dem eine Therapie mit Ritalin bislang kaum Besserung gebracht hat, gibt es die Möglichkeit eines Eintritts in eine klinische Studie, in der eine neue pharmakologische Substanz mit grossem Potential getestet werden soll. Das Studiendesign sieht vor, dass Peter regelmässig diese neue Substanz erhalten soll und im Verlauf der Studie fMRI-Scans unterzogen würde, um einfache Aufgaben im Scanner zu lösen. Dies natürlich nur auf der Grundlage, dass die medikamentöse Therapie greift, da ansonsten die 20-minütige Aufgabe im Scanner aus ärztlicher Sicht Peter nur unnötig belasten würde. Die Eltern werden mit folgenden Informationen versehen: eine Angabe über die potentiellen Nebenwirkungen der Substanz, die Freiwilligkeit des Eintritts in diese Studie, sowie die Möglichkeit, jederzeit und ohne Angabe von Gründen aus der Studie austreten zu dürfen, ohne dass ihm daraus Nachteile für die sonstige Behandlung erwachsen. Nach Einwilligung der Eltern und Beginn der Studie verbessern sich Peters Konzentrationsfähigkeiten. Im fMRI-Scan stellen die Ärzte jedoch dann eine Anomalie im Bereich des Frontalhirns fest, hervorgerufen allenfalls durch eine frühkindliche Hirnblutung. Nun wird diskutiert, ob Peter besser von der Studie ausgeschlossen werden soll, weil die Aussagekraft der Studie beeinträchtigt werden könnte. Auf welche Aspekte soll die Expertengruppe bei der Untersuchung dieser Sachlage achten?

Selected Vignettes (in English; translation has not been reviewed (i.e. no back-translation has been performed)):

Vignette 1:

Dr. P, an experienced oncologist in hospital X has previously received several offers from various other hospitals. So far, he always declined these offers because of his relatedness to his hospital and due to his housing situation. However, for some time, internal disagreements between him, as a director of the oncology unit, and the clinical director, emerged. They concern student-based education modalities, patient-oriented information requirements and the set-up of a palliative care unit towards which Dr. P. has a critical stance. Since the untimely death of his wife, Dr. P. is even more engaged towards the patients in his unit. Simultaneously, his skepticism towards innovation increased. This resulted in several conflicts with other senior physicians. Negotiations with the executive board of the hospital and the other senior physicians regarding the mentioned issues are currently underway. Among other things, the clinic director is considering whether Dr. P. should be dismissed due to the disturbed harmony within the hospital and the lack of consensual procedures. How should the clinic management evaluate this situation?

Vignette 3:

Miss J., a middle-aged patient has to undergo surgery following ankle injury. Although being a routine operation, the senior surgeon is performing the surgery because of insurance modalities. The day after surgery, the exit interview takes place in the presence of the senior surgeon and the nurse. The senior physician explains the importance of thrombosis prophylaxis and the procedure of subcutaneous heparin-injection by means of a thin needle, similar to insulin self-application. Four days after having left the hospital, the patient is transferred to the hospital for emergency medical treatment due to respiratory dysfunction and cardiac arrhythmia. Immediately, a pulmonary emoblism is diagnosed. The emergency doctor assumes an insufficient thrombosis prophylaxis being the cause for the lung embolism. Subsequent enquiries revealed that the patient apparently was insecure regarding the procedure of heparin-injection. A subsequent discussion with the senior physician revealed no clarification of the situation. Usually the nurse explains the thrombosis prophylaxis. In the current situation however, the senior physician apparently has taken over this task. The clinic management now has to examine the case and has to evaluate the course of action of the personnel. On which aspects should they focus?

Vignette 5:

A 65 years old eccentric artist has been admitted to a nursing home as a consequence of increasingly frequent episodes of dementia. It quickly becomes clear that there is still a need for him to express himself through his passion for art, particularly evidenced by a permanent mentioning of his desire. Even though the handling of the artist often was challenging for the nurses due to his distinctive personality and his desire for artwork, he otherwise is described as a solitary, introverted and relatively calm home resident. Recently, he pushes forward the idea of establishing a studio in the hobby room of the nursing home in order to live out his desire for artwork. Some of the other residents support this idea. However, as the construction of a studio would imply several restructuring work and due to staff planning and potential long-term consequences, the personnel is hesitant regarding this idea. How should the management of the nursing home evaluate this situation?

Vignette 6:

Professor M., a member of the expert committee, is a renowned scientist in the field of migraine and pain research. She reports that she recently attended a congress, where a new clinical study testing a promising drug for migraine has been presented. In this presentation of the study, it was mentioned that the drug might induce side-effects including digestive dysfunctions. However, these normally disappear during long-term use. Prof. M. has been asked by the study director, whether she would be able to recruit patients for the study. After the return of the congress, a 45 years old patient was reported to Prof. M. for consultation. Miss P., the patient, is a socially engaged person suffering since the age of 35 from recurrent, regularly appearing migraine. Miss P. is often unable to work and to take care of her personal duties due to the re-emerging migraines. Prof. M. informs the patient routinely about the study design. Showing great interest in the study, the patient considers entering it. Prof. M. is confident to be able to secure a spot in the study because of her contacts to the study director. She now asks the expert committee regarding her information requirements between patient and study-team. On which aspects should the expert committee pay attention?

Vignette 7:

Peter, a 10 years old patient suffering from ADHD for whom a therapy including Ritalin has largely failed, would have the possibility to enter a clinical study testing a new pharmacological compound with great potential. The study design envisages a regular intake of this new substance combined with fMRI-scans during which Peter is supposed to solve a simple task. The 20-minutes fMRI task is only permissible from a medical point of view, if the pharmacological therapy shows beneficial effects; otherwise, the procedure would be an unnecessary burden for Peter. The parents are provided with the following information: details on possible side-effects of the drug, the voluntariness of study entrance and the possibility to quit the study any time without the need of stating reasons and with no disadvantages with respect to other medical treatments. After parental approval the concentration abilities of Peter improve. In the fMRI-scan the physicians however detect a malformation situated in the region of the frontal brain, possibly caused by an early childhood cerebral hemorrhage. Now the debate concerns whether Peter should better be excluded from the study because of impairment of the study's conclusiveness (significance/validity of the study). On which aspects should the expert committee pay attention when investigating this situation?

Outlook

The immense advances which were achieved in neuroscientific research and therapy together with the incredible public awareness of the field substantiate neuroscience as a leading discipline at the interface between medicine and natural science. Undoubtably, such a stance also bears the danger of distraction from challenges neuroscience is confronted with. Challenges include the anticipated understanding of the functioning of complex living systems together with the causes and mechanisms of neurological and psychiatric disorders. Given these inherent challenges and limitations, any (clinical) neuroscientist knowing about the often easily and rapidly sparking euphoria emanating from preliminary research results or treatment successes has to be able to take both a critical and humble view all at once. Like in no other area of medicine, self-criticism and humility are leading personality traits.

Notable is one strain of research which is currently in progress. We are in the process of investigating on the electric field expansion based on a physics-informed theoretical model which takes into account regional anatomical and physiological characteristics. By making a statement about the general shape and size of the electric field in tissue we claim to being able to contribute to the question of how to minimize side effects and complications. Hence, combined with the translation of the instrument for measuring moral behavioural changes, enriched with carful normative reflection, we tackle the issue of behavioural and personality-related side-effects from three different angles, which again reflects the nature of DBS as a whole, a truly multidisciplinary journey.

At the end I hope I have succeeded in showing that in the process of evaluating interventions into the brain partly resulting in personality-changes, a theoretical and empirical understanding of such changes is indispensable. In summary, instead of metaphysical thought-experiments, more empirical research is required to better understand how interventions into the central nervous system can result in feelings of alienation, inauthenticity and complex personality changes and how one is able to help those patients. It is important to appreciate that deep brain stimulation is as much a therapy as a tool of discovery, and to secure the resources that will allow us to develop treatments and imagine next-generation hypotheses to serve patients now and in the future (Fins, J. J., Mayberg, H. S., & Schlaepfer, T. E. (2011). FDA Exemptions: The Authors Reply. Health Affairs).

I end this cumulative dissertation by quoting Montogmery (Montgomery Jr, E. B. (2010). Deep brain stimulation programming: principles and practice):

> *"At the time of neurobiological hegemony in the construction of models of neurological and mental disorders in particular, it may be the critique that careful analysis can bring to this modeling process and the refusal to abandon alternative explanatory constructs that may be philosophy's most valuable contribution".*

Christian Ineichen

Profile

My fields of interest include the intersection of clinical neurology, experimental neurobiology and psychiatry in general, empirical bioethics, neuroethics, the psychological and neural basis of moral behaviour, philosophy of psychiatry and philosophy of mind. More specifically, I'm interested in translational and interdisciplinary research of Deep Brain Stimulation (DBS) and other forms of neuromodulation. In February, I completed the PhD-Program of the Institute of Biomedical Ethics and History of Medicine. Simultaneously, I completed the international PhD Program in Neuroscience, ZNZ, at the UZH/ETH in Zurich. I currently work on deep brain stimulation (modelling the electric field expansion) and the development of a tool for measuring moral competencies.

Education

02/2016–current **Post-doctoral research fellow**, *University of Zurich*, Zurich, Switzerland.

09/2011–02/2016 **Ph.D.**, *University of Zurich*, Zurich, Switzerland, *Clinical and ethical aspects of modulating behaviour and affect through Deep brain stimulation.*
Supervisors: PD Dr. M. Christen (UZH), Prof. Dr. med. C. Baumann (USZ), Dr. med. O. Sueruecue (USZ), Prof. Dr. med. Dr. phil. N. Biller-Andorno (UZH)

05/2014–ongoing **Research assistant**, *University Hospital Zurich, USZ*, Zurich, Switzerland, CRPP Sleep and Health, Prof. Dr. med. Christian Baumann and Dr. Daniela Noain, Department of Neurology, translational DBS, electric field simulation, parameter selection.

04/2013–12/2013 **Research assistant**, *Swiss Federal Institute of Technology, ETH*, Zurich, Switzerland, Institute of molecular systems biology, Prof. Dr. E. Hafen, in collaboration with the Institute of Biomedical Ethics, Dr. E. Vayena, statistics.

09/2011–03/2012 **Research assistant**, *University of Zurich*, Zurich, Switzerland, Institute for banking and finance, Prof. Dr. C. Tanner, Director of "Center for Responsibility in Finance" in the field of Moral/Ethical Decision Making and Behavior.

05/2011–05/2012 **Research assistant**, *University of Zurich*, Zurich, Switzerland, University of Zurich, Preclinical Laboratory for Translational Research into Affective Disorders(PLaTRAD) Clinic for Affective Disorders and General Psychiatry Psychiatric University Hospital Zurich, Prof. Dr. C. Pryce.

10/2005–04/2011 **Master of Science, University of Zurich in Neuroscience**, *University of Zurich*, Zurich, Switzerland, *Major: Master of Neuroscience, Minor in Biochemistry, concomitant studies in philosophy.*
Supervisor: Prof. Dr. C. Pryce (University of Zurich, Preclinical Laboratory for Translational Research into Affective Disorders(PLaTRAD) Clinic for Affective Disorders and General Psychiatry Psychiatric University Hospital Zurich)

08/2000–07/2005 **High School ("Gymnasium")**, *FKSZ, Matura profile: modern languages*, Zurich, Switzerland.

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Theses

PhD thesis

Title	*Clinical and ethical aspects of modulating behaviour and affect through Deep Brain Stimulation*
Supervisors	PD Dr. M. Christen (UZH), Prof. Dr. med. C. Baumann (USZ), Dr. med. O. Sueruecue (USZ), Prof. Dr. med. Dr. phil. N. Biller-Andorno (UZH)
Keywords	deep brain stimulation, behaviour, affect, neuroethics

Master thesis

Title	*Probabilistic reversal learning in mice: establishing a task and assessing serotonin effects using genetic and pharmacological methods*
Supervisor	Prof. Dr. C. Pryce
Keywords	Mouse, Probabilistic reversal learning, Reward, Punishment, Expectancy/prediction, Serotonin, Escitalopram, Depression

Experience

2013 **Assistant and coordinator**, *University of Zurich*, Neuroethics spring and summer school.
Organizing and presenting; school for international PhD students

2013 **Assistant**, *University of Zurich*, Lecture for medical students: Modul: Mantelstudium Menschenbilder Medizin.

Languages

German	**native tongue**
English	**fluent**
French	**good**
Italian	**good**

Skills

Quantitative bioethics, psychological instrument development, moral psychology

Operant conditioning, behavioral tests

Psychopharmacological manipulations, stereotactic neurosurgery, immunohistochemistry, neuroanatomy of neuronal circuits

SPSS statistical analysis (descriptive data analysis, t-tests, ANOVA, correlation and regression analysis, clusteranalysis, MDS, factor analysis, nonparametric tests, quality control), other quantitative research methods (bibliometrics)

Experience with the programming language Python

Voluntary Work

2004 – present **Dipl. Personal Trainer**, *SAFS*.
Focus: Workout training

Interests

Sports/Leisure workout training, fitness, biking, reading

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Leisure reading

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Talks

-Designing Moral Technologies – Theoretical, Practical and Ethical Issues, Monte Verita, Ascona, Switzerland July 10-15, 2016

-NCCR Molecular Systems Engineering Fellows Retreat, Magglingen, Switzerland, 20 – 22 April, 2016

-Annual meeting of the international neuroethics society and the annual meeting of neuroscience of the society for neuroscience, Chicago, USA, 15 – 21 October, 2015

-NCCR Molecular Systems Engineering Fellows Retreat, Riederalp, Switzerland, 15 – 17 April, 2015

-International Conference on Deep Brain Stimulation - 25 years -, Düsseldorf, Germany, 30 – 31 May, 2013

Publications

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Effy Vayena, Christian Ineichen, Elia Stoupka, and Ernst Hafen. Playing a part in research university students' attitudes to direct-to-consumer genomics. *Public health genomics*, 17(3):158–168, 2014.

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